

**Advisory Committee Industry Briefing Document**  
**Testosterone Replacement Therapy**

**Bone, Reproductive and Urologic Drugs Advisory  
Committee and the Drug Safety and Risk  
Management Advisory Committee**

**Meeting on September 17, 2014**

## Table of Contents

<b>1.0</b>	<b>Executive Summary.....</b>	<b>8</b>
<b>2.0</b>	<b>Testosterone Replacement Therapy: Regulatory History .....</b>	<b>11</b>
2.1	Approval History in the United States .....	11
2.2	Requirements for Regulatory Approval .....	12
2.3	Indication .....	13
2.4	Safety Labeling .....	14
2.5	Current Regulatory Activities .....	15
<b>3.0</b>	<b>Testosterone, Hypogonadism, Guidelines, and Testosterone Replacement Therapy Benefits .....</b>	<b>16</b>
3.1	Testosterone .....	16
3.2	Hypogonadism .....	19
3.2.1	Classification, Signs, and Symptoms of Hypogonadism .....	19
3.2.2	Prevalence of Hypogonadism .....	22
3.2.3	Comorbid Conditions.....	26
3.2.4	Endocrine Society Guidelines.....	26
3.3	Testosterone Replacement Therapy .....	28
3.3.1	Introduction.....	28
3.3.2	Limitations of Literature Evaluating Benefits of Testosterone Replacement Therapy .....	28
3.4	Effects of Testosterone Replacement in Hypogonadal Men.....	29
3.4.1	Benefits Related to Lean Mass, Muscle Strength, and Fat Mass.....	30
3.4.2	Benefits Related to Bone Mineral Density and Bone Architecture .....	33
3.4.3	Benefits Related to Sexual Function.....	36
3.4.4	Benefits Related to Fatigue .....	38
3.4.5	Benefits Related to Mood and Cognition.....	40
3.4.6	Benefits Related to Special Populations .....	42
3.4.6.1	Metabolic Syndrome and Type 2 Diabetes Mellitus.....	42
3.4.6.2	Human Immunodeficiency Virus.....	45
3.4.6.3	Additional Special Populations.....	46
3.5	Limitations and Uncertainties for the Evidence of Benefit.....	46

3.5.1	Late Onset Hypogonadism (Androgen Deficiency of the Aging Male) .....	46
3.6	Ongoing Studies .....	47
3.7	Summary: Hypogonadism, Guidelines, and Benefits of Testosterone Replacement Therapy .....	48
<b>4.0</b>	<b>Cardiovascular Risk in Hypogonadal Men.....</b>	<b>50</b>
4.1	Cardiovascular Risk Introduction .....	50
4.2	Cardiovascular Background.....	52
4.3	Incidence and Prevalence of Cardiovascular Events .....	54
4.3.1	Cardiovascular Events in the Hypogonadal Male Population .....	56
4.4	Risk Factors for Cardiovascular Events.....	59
4.5	Associations Between Hypogonadism and Cardiovascular Events.....	59
4.5.1	Type 2 Diabetes Mellitus, Obesity and Metabolic Syndrome, Hypertension, and Hyperlipidemia .....	59
4.5.2	Coronary Artery Disease.....	60
4.5.3	Cardiovascular and All-Cause Mortality .....	62
4.6	Evaluation of Testosterone Replacement Therapy and Cardiovascular-Related Events .....	65
4.6.1	Placebo-Controlled Studies .....	65
4.6.2	Meta-Analyses of Testosterone Replacement Therapy and Cardiovascular Events or Cardiovascular Risk Factors.....	67
4.6.2.1	Meta-Analyses of Testosterone Replacement Therapy and Cardiovascular Events .....	70
4.6.2.2	Meta-Analyses of Testosterone Replacement Therapy and Cardiovascular Risk Factors .....	74
4.6.3	Observational Studies .....	75
4.7	Evaluation of Testosterone Replacement Therapy and Cardiovascular Risk Factors .....	84
4.8	Summary .....	90
<b>5.0</b>	<b>Drug Utilization .....</b>	<b>92</b>
5.1	Drug Utilization Introduction .....	92
5.2	Background: Prevalence of Hypogonadism and Common Comorbid Conditions.....	93
5.3	Prescription Trends over Time for Testosterone Products .....	93

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5.4	Prescribing Patterns by Physician Specialty .....	96
5.5	Age Distribution of Patients Receiving Testosterone Replacement Therapy .....	98
5.6	Characteristics of Patients Receiving Testosterone Replacement Therapy .....	100
5.7	Reported Diagnostic Codes for Patients Who Receive Testosterone Replacement Therapy .....	101
5.8	Presence of Testosterone Values Prior to Starting Testosterone Replacement Therapy .....	103
5.9	Persistence of Testosterone Replacement Therapy Use .....	105
5.10	Summary of Utilization Data .....	105
<b>6.0</b>	<b>Conclusions.....</b>	<b>107</b>
<b>7.0</b>	<b>References.....</b>	<b>110</b>

## List of Tables

Table 1.	FDA-Approved Branded Testosterone Products Currently Marketed in the United States .....	12
Table 2.	Classification of Male Hypogonadism.....	21
Table 3.	Estimation of Prevalence of Testosterone Deficiency .....	24
Table 4.	Strengths and Limitations of Changes in Fat Mass, Lean Mass, and Muscle Strength .....	32
Table 5.	Strengths and Limitations of Changes in Bone Mineral Density.....	36
Table 6.	Mean $\pm$ SD Difference on Total and Domain Score of the International Index of Erectile Function (IIEF-15) Between the Testosterone and Placebo Groups .....	37
Table 7.	Strengths and Limitations of Changes in Sexual Function .....	38
Table 8.	Strengths and Limitations of Changes in Fatigue .....	40
Table 9.	Strengths and Limitations of Changes in Mood and Cognition.....	42
Table 10.	Strengths and Limitations of Improvements in Glycemic Control in Metabolic Syndrome and Type 2 Diabetes Mellitus .....	45
Table 11.	Strengths and Limitations of Testosterone Replacement Therapy in HIV-Infected Males .....	46
Table 12.	Annual Rates of Heart Failure per 1,000 Population in 2006.....	55

Table 13.	Cardiovascular Events in the Hypogonadal Male Population .....	57
Table 14.	Summary of Studies Reporting on Low Testosterone and Coronary Artery Disease.....	61
Table 15.	Association of Testosterone Levels with Cardiovascular and All-Cause Mortality <sup>a</sup> .....	63
Table 16.	Published Meta-Analyses of Studies Examining Testosterone Replacement Therapy and Broadly Defined Cardiovascular- Related Events .....	68
Table 17.	Rates of MI per 1,000 PY in All Men, Men Aged 65 Years, and Men Aged > 65 Years in Pre- and Post-Prescription Interval for Initial Testosterone Replacement Therapy Versus PDE5i.....	80
Table 18.	Rates of MI per 1,000 PY Pre- and Post-Index Intervals for Initial Testosterone Replacement Therapy Prescription or First Randomly Assigned Date of Diagnosis with Hypogonadism Without a Testosterone Replacement Therapy Prescription.....	80
Table 19.	Published Meta-Analyses of Studies Examining Testosterone Replacement Therapy and Risk Factors for Cardiovascular Disease .....	86
Table 20.	Number of Testosterone Replacement Therapy Prescriptions by Patient Age (2009 to May 2014).....	99
Table 21.	Most Common Diagnosis Codes for Patients with a Testosterone Replacement Therapy Prescription (2006 to May 2014, N = 2,923,500) .....	102

## List of Figures

Figure 1.	Prevalence of Low Testosterone in Aging Men.....	19
Figure 2.	Effects of Testosterone Replacement Therapy on Strength in the Leg-Press and Chest-Press Exercises and on Loaded Stair- Climbing Power in the Testosterone in Older Men (TOM) Trial .....	32
Figure 3.	Effects of Testosterone on Bone Density Measured as Mean Difference on Absolute Values (Panel A) and Reported as Percentage Change from Baseline at Lumbar Spine (Panel B) .....	35
Figure 4.	Weighted Differences of Mean HbA <sub>1c</sub> (Panel A), Fasting Glycemia (Panel B), Triglycerides (Panel C), and Fat Mass (Panel D) Across Randomized Controlled Trials .....	43

Figure 5.	Forest Plots of Placebo-Controlled Randomized Trials Examining the Pooled Effect of Testosterone Replacement Therapy on Cardiovascular-Related Events .....	73
Figure 6.	Myocardial Risk Rate 1 Year Prior to and 1 Year After Index Date .....	81
Figure 7.	Volume of Prescriptions by Month, January 2000 to July 2014.....	95
Figure 8.	Number of Prescriptions by Specialty .....	97
Figure 9.	Percentage of Claims that Had a Diagnosis of Hypogonadism in Patients Who Received a Prescription of Testosterone Replacement Therapy .....	103

## List of Appendices

Appendix A.	Cardiovascular Events in the General Population.....	139
Appendix B.	Summary of Studies Discussed Within the Cardiovascular Risk Section.....	145
Appendix C.	Summary of Studies Reporting Effects of Testosterone Replacement Therapy on Lipids, Cholesterol, and Triglycerides.....	149
Appendix D.	Description of the National Prescription Audit.....	151
Appendix E.	Testosterone Replacement Therapy Prescription Volume by Specialty Group, 2009 – May 2014 .....	153
Appendix F.	Description of SHA's Integrated Dataverse (IDV) .....	156

### **List of Abbreviations**

ADAM	Androgen Deficiency in Aging Males
AHA	American Heart Association
AIDS	Acquired immunodeficiency syndrome
AP	Angina pectoris
ARIC	Atherosclerosis and Risk in Communities
BLSA	Baltimore Longitudinal Study of Aging
BMD	Bone mineral density
BMI	Body mass index
CAD	Coronary artery disease
CCS	Case control study
CDM	ClinformaticsDataMart
CHD	Coronary heart disease
CI	Confidence interval
C <sub>max</sub>	Maximal plasma concentration
COPD	Chronic obstructive pulmonary disease
CV	Cardiovascular
CVD	Cardiovascular disease
DHT	5 dihydrotestosterone
DSMB	Data safety monitoring board
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GnRH	Gonadotropin-releasing hormone
HbA <sub>1c</sub>	Glycosylated hemoglobin
HDL	High-density lipoprotein
HED	Hypogonadism Energy Diary
HF	Heart failure
HIM	Hypogonadism in Males
HIS-Q	Hypogonadal Impact of Symptoms Questionnaire
HIV	Human immunodeficiency virus
HR	Hazard ratio
HTN	hypertension
IDV	[SHA's] Integrated Dataverse

IIEF	International Index of Erectile Function
IM	Intramuscular
IND	Investigational new drug application
LDL	Low-density lipoprotein
LH	Luteinizing hormone
LHRH	Luteinizing hormone-releasing hormone
MACE	Major adverse cardiac event
MI	Myocardial infarction
MMAS	Massachusetts Male Aging Study
NDA	New drug application
NH	Non-Hispanic
NHLBI	National Heart, Lung, and Blood Institute
NPA	[IMS] National Prescription Audit™
OR	Odds ratio
PCP	Primary care physician
PDE5i	Phosphodiesterase type 5 inhibitor
PK	Pharmacokinetics
PY	Person year
RCT	Randomized clinical trial
RR	Relative risk
SAE	Serious adverse event
SAID	Sexual Arousal, Interest and Drive
SD	Standard deviation
SHA	Source Health Care Analytics
SHBG	Sex hormone-binding globulin
T2DM	Type 2 diabetes mellitus
TOM	Testosterone in Older Men
TRiUS	Testim Registry in the United States
TRT	Testosterone replacement therapy
T Trial	The Testosterone Trial
UK	United Kingdom
US	United States
VA	Veterans Affairs
VTE	Venous thromboembolism



## 1.0 Executive Summary

Testosterone products have been approved in the United States (US) for over 50 years, and indications include the treatment of primary hypogonadism and hypogonadotropic hypogonadism (congenital or acquired) in males.

Hypogonadism is an endocrine disorder characterized by absent or deficient testosterone levels along with signs and symptoms of androgen deficiency. The absence or deficiency of testosterone is associated with regression of secondary sexual characteristics, impaired sexual function, impaired sense of well-being, muscle wasting and decreased strength, and reduced bone mineral density.

Current guidelines for use of testosterone replacement therapy (TRT) outline the appropriate assessment and monitoring for men who are candidates for testosterone therapy. Key components of the Endocrine Society Guidelines<sup>1</sup> include selecting candidates with consistent signs and symptoms of hypogonadism and documented evidence of low testosterone levels. Confirmatory testing of testosterone and additional evaluation is also recommended, along with a treatment plan.

Two publications, Vigen et al.<sup>2</sup> and Finkle et al.,<sup>3</sup> posed questions regarding the cardiovascular (CV) safety of TRT, particularly in elderly men and those with a prior history of CV disease. These two publications also formed the basis for the Food and Drug Administration (FDA) to post a Drug Safety Communication (January 31, 2014), regarding their ongoing evaluation of the potential risk of stroke, heart attack, and death in men taking FDA-approved testosterone products.

On the basis of these publications and other information, the FDA scheduled an Advisory Committee Meeting for September 17, 2014, to "discuss the appropriate indicated population for testosterone therapies and the potential for cardiovascular risk associated with this use." This briefing book is being provided by the TRT Sponsors (Section 2.5), to provide the industry perspective for the discussion at this Advisory Committee Meeting. The briefing book provides a review, by the TRT Sponsors, of the available

literature and other data with regard to potential benefits of TRT, CV safety of TRT, and utilization data for TRTs.

A comprehensive review of the literature regarding potential benefits of TRT was undertaken. Although benefits have been observed across numerous published studies, there are limitations to these data sets, and these are discussed within the briefing book. One limitation is the relative absence of large controlled long-term studies, which makes it difficult to interpret the long-term clinical impact of TRT.

Nevertheless, the data consistently support TRT benefits on measures of lean mass, fat mass, and bone mineral density and architecture. Less consistently, data also suggest benefit with sexual function. Additionally, there is some evidence that suggests benefit with mood and fatigue.

In summary, the totality of data supports benefits on a number of hypogonadal signs and symptoms with TRT in hypogonadal men.

The CV risk profile in hypogonadal individuals receiving TRT was extensively reviewed by the TRT Sponsors. A limitation of the literature is the relative absence of large controlled long-term studies.

That said, based on a systematic review of the of the available literature, the TRT Sponsors found insufficient evidence to support an association between testosterone use and an increased risk of CV events. However, the TRT Sponsors also recognize that continued active surveillance is required given the questions raised, particularly in certain subpopulations such as elderly men and/or patients with preexisting CV disease.

Lastly, the TRT Sponsors reviewed information regarding usage patterns for TRT, including trends in prescribing patterns of testosterone products, as well as characteristics of patients receiving TRT.

It was observed that the number of TRT prescriptions has consistently increased from 2000 through 2013 and that primary care physicians (PCPs) make up the majority of

prescribers (approximately 60%). Men aged 45 to 64 years old received the highest number of prescriptions (approximately 60%), with men younger than 45 years and men over 65 years making up 19% and 21% of prescriptions, respectively. The typical length of treatment for testosterone products has been reported to be between 3 and 4 months.

Additional characterization of men using TRT was limited by the ability of the available data sources to address these questions. Some data on etiology of hypogonadism or signs and symptoms is available, but the generalizability of this information is unknown. In terms of diagnostic codes related to hypogonadism in patients who received TRT, in one database study, 43% of patients had relevant diagnostic code indicative of hypogonadism; but this study has limitations that may make this a conservative estimate. The percentage of patients receiving TRT who have baseline serum testosterone laboratory values is variable based on available literature.

In summary, limitations in the available utilization data make it difficult to fully characterize the population of men taking TRT and to evaluate the degree to which the current use aligns with approved labeling. Specifically, the utilization data lack diagnostic codes for indications. Further, the data suggest that the practice of laboratory testing including pre- or post-testosterone serum levels is inconsistent.

The TRT Sponsors remain committed to educating clinicians and patients on the benefits and risks of TRT, so that they can make informed treatment decisions. To maximize the benefits of TRT and mitigate potential risks, the TRT Sponsors plan to discuss a number of potential activities at the September Advisory Committee Meeting.

For instance, the TRT Sponsors will partner with professional societies (such as the Endocrine Society) regarding current practices for diagnosis, patient selection, and management, and to continue communicating and educating clinicians and patients on the appropriate use of these products. Further efforts could include targeted training (for instance, to select prescriber groups) and, if appropriate, revising product labeling.

As the TRT Sponsors consider this information, it is worth recognizing that the scientific understanding of benefits and risks of TRT, broadly and in special populations, continues to advance as new data become available. For instance, the Testosterone Trial (T Trial), designed to characterize the benefits of testosterone use in older men, will also provide relevant information on safety. Furthermore, guidelines for TRT use may be further refined as new data become available.

## **2.0 Testosterone Replacement Therapy: Regulatory History**

### **2.1 Approval History in the United States**

In 1953, the FDA approved Delatestryl<sup>®</sup>, the first formulation of testosterone enanthate for intramuscular (IM) injection. Subsequently, other esters of testosterone, such as testosterone cypionate and testosterone propionate, were approved by FDA for IM administration. Testopel<sup>®</sup> (pellets for subcutaneous implantation) was approved in 1972. Testoderm<sup>®</sup> and Androderm<sup>®</sup>, approved in 1993 and 1995, respectively, are transdermal patches. Topical gels such as Testim<sup>®</sup>, AndroGel<sup>®</sup>, and Fortesta<sup>®</sup>, and Vogelxo, and the topical solution Axiron<sup>®</sup> have followed ([Table 1](#)). Striant<sup>®</sup>, a testosterone buccal system, was approved in 2003. In 2014, the FDA approved an intranasal gel, Natesto<sup>®</sup>, and an injectable formulation with reduced dosing frequency, Aveed<sup>®</sup>. In addition to branded testosterone products ([Table 1](#)), numerous generic versions of different formulations are also available in the US. Testosterone replacement therapies are indicated for adult males with conditions associated with a deficiency or absence of endogenous testosterone.

**Table 1. FDA-Approved Branded Testosterone Products Currently Marketed in the United States**

Trade Name	TRT Sponsor	Route of Administration	NDA	Date of Approval
Delatesteryl	Endo Pharmaceuticals	Injection	9,165	24 December 1953
Testopel	Auxilium	Pellet for implantation	ANDA 80,911	13 July 1972
Androderm	Watson	Transdermal patch	20,489	29 September 1995
AndroGel 1%	AbbVie	Transdermal gel	21,015	28 February 2000
Testim	Auxilium	Transdermal gel	21,454	31 October 2002
Striant	Auxilium	Buccal system	21,543	19 June 2003
Axiron	Eli Lilly and Company	Topical solution	22,504	23 November 2010
Fortesta	Endo Pharmaceuticals	Transdermal gel	21,463	29 December 2010
AndroGel 1.62%	AbbVie	Transdermal gel	22,309	29 April 2011
Aveed	Endo Pharmaceuticals	Injection	22,219	5 March 2014
Natesto	Trimel Biopharma SRL	Nasal gel	205,488	28 May 2014
Vogelxo	Upsher-Smith	Transdermal gel	204,399	4 June 2014

ANDA = abbreviated new drug application; NDA = new drug application

## 2.2 Requirements for Regulatory Approval

To date, the FDA has generally approved TRT products on the basis of restoring blood testosterone levels to the eugonadal range in a single pivotal open-label clinical trial. The current primary efficacy endpoint is defined as 75% of subjects with serum total testosterone  $C_{avg}$  (0 – 24 hours) on a predefined pharmacokinetic (PK) day within the normal range of 300 to 1,000 ng/dL. In addition, the lower bound of the 2-sided 95% confidence interval (CI) cannot be less than 65% based on PK results.

A critical secondary efficacy endpoint is total testosterone maximal plasma concentration ( $C_{max}$ ) values during the study. The individual total testosterone  $C_{max}$  values must be within the following ranges:

C<sub>max</sub> 1,500 ng/dL in 85% of the subjects

C<sub>max</sub> between 1,800 and 2,500 ng/dL in 5% of the subjects

C<sub>max</sub> > 2,500 ng/dL in no subjects

## 2.3 Indication

In 1981, the FDA issued the Androgen Class Labeling Guideline, which provided an *Indications and Usage* statement for hypogonadism in many testosterone products, including Delatestryl, still use [Androgen Class Labeling Guideline 1981]:

*"Androgens are indicated for replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone.*

- a. Primary hypogonadism (congenital or acquired)-testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, or orchidectomy.*
- b. Hypogonadotropic hypogonadism (congenital or acquired)--idiopathic gonadotropin or LHRH deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation."*

All approved testosterone products, beginning with the 2002 Testim approval, have the following indication statement with distinctions between products as indicated in brackets and underlined:

*DRUG is [an androgen] indicated for replacement therapy in [adult] males for conditions associated with a deficiency or absence of endogenous testosterone:*

*Primary hypogonadism (congenital or acquired): testicular failure due to [conditions such as] cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchidectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range.*

*Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations, but have gonadotropins in the normal or low range.*

The FDA describes hypogonadism in publicly available NDA review documents as follows [NDA 21015 AndroGel 1% FDA Medical Review. 2000]:

*"The term 'male hypogonadism' refers to a condition in which the endogenous secretion of testosterone is 'insufficient' or 'inadequate' to maintain serum testosterone levels within the normal range. Some symptoms which may be associated with this condition include decreased sexual desire, changes in mood, regression of male secondary sex characteristics, and fatigue. It is also possible that prolonged hypogonadism may lead to osteoporosis. Some conditions which may lead to a hypogonadal state in men include cryptorchidism, bilateral testicular torsion, orchitis, Klinefelter's Syndrome, exposure to chemotherapy or heavy metals ('primary hypogonadism') and pituitary-hypothalamic injury secondary to radiation, trauma, tumors or other idiopathic causes ('hypogonadotropic hypogonadism')."*

## **2.4 Safety Labeling**

Most testosterone product safety labeling is class labeling resulting from the pharmacologic characteristics of testosterone and its mode of action. Testosterone products are contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate, as well as in women who are or may become pregnant, or who are breastfeeding.

Regarding the potential CV risks of TRT, the labeling for most testosterone products contain information directly or indirectly related to cardiovascular disease, including edema, congestive heart failure, lipid changes, sleep apnea, blood pressure changes, glucose changes, and increases in red blood cell mass. However, some variations in safety labeling exist between different formulations and dosage forms.

Additional safety risks reflected in the *Warnings and Precautions* sections of all testosterone products include potential increases in benign prostatic hyperplasia, polycythemia, postmarketing reports of venous thromboembolism (VTE), virilizing effect, potential effect on spermatogenesis, sodium retention, edema with or without congestive heart failure, gynecomastia, sleep apnea, changes in lipid profile, hypercalcemia, and decreased thyroxine-binding globulin. A hepatic adverse event *Warning*, although specific to oral 17-alpha-alkyl androgens, is also included in the labeling of all testosterone products, even those that are not 17-alpha-alkylated products. Variations in safety labeling exist between dosage forms that result from the unique safety concerns related to specific formulations.

## **2.5 Current Regulatory Activities**

On January 31, 2014, FDA issued a Drug Safety Communication informing the public of its investigation of "the risk of stroke, heart attack, and death" in men taking FDA-approved testosterone products. FDA has not concluded that FDA-approved testosterone treatment increases the risk of these events. On July 14, 2014, FDA announced its intent to hold a joint meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, scheduled for September 17, 2014. The Advisory Committee meeting will discuss the appropriate indicated population for TRT and the potential for adverse CV outcomes associated with this use.

As requested by the FDA, 12 TRT Sponsors of testosterone Investigational New Drug applications (INDs) and New Drug Applications (NDAs) are collaborating to present the Industry perspective on the following topics:

The current use of testosterone in clinical practice, including:

Demographics of patients receiving testosterone prescriptions, including extent of testosterone use by age;

Clinical characteristics of patients receiving testosterone currently, including the reasons for use;



Scientific evidence supporting benefit with these current uses; and  
The potential for CV risk associated with these current uses.  
Whether the approved labeling for testosterone products, including the  
approved indication, reflects the population and current reasons for use of  
testosterone.

This briefing book is a consensus document reflecting the views of the 12 collaborating TRT Sponsors on the above topics. The following TRT Sponsors have contributed to this briefing book:

AbbVie  
Auxilium Pharmaceuticals, Inc. (Auxilium)  
Besins Healthcare  
Clarus Therapeutics  
Eli Lilly and Company (Lilly)  
Endo Pharmaceuticals  
Lipocine  
MonoSol Rx  
TesoRx  
Trimel Pharmaceuticals  
Upsher-Smith Laboratories  
Viramal

### **3.0 Testosterone, Hypogonadism, Guidelines, and Testosterone Replacement Therapy Benefits**

#### **3.1 Testosterone**

Testosterone, the most abundant circulating androgen in men, is primarily produced by Leydig cells of the testes; it is also produced by the adrenal glands in males and females.<sup>4</sup> Testosterone secretion is regulated by negative feedback interactions within the hypothalamic pituitary-testicular axis.<sup>5</sup> In the healthy adult male, the hypothalamus

releases gonadotropin-releasing hormone (GnRH) in a pulsatile fashion, which then stimulates the pulsatile release of luteinizing hormone (LH) and, to a lesser extent, follicle-stimulating hormone (FSH) from the pituitary gland.<sup>6,7</sup> Pulsatile LH stimulates Leydig cells to produce testosterone; testosterone is broken down into its metabolites DHT and estradiol, which then exert negative feedback on GnRH and gonadotropin secretion.<sup>5,8,9</sup>

Testosterone can act directly on target tissues or through its conversion to 5 dihydrotestosterone (DHT) on androgen receptors present in reproductive and nonreproductive tissues.<sup>10</sup> In addition, testosterone can be converted to estradiol via the aromatase enzyme both in the testis and peripherally and can act through interaction with estrogen receptors.<sup>10</sup> Testosterone secretion varies throughout the day, with concentrations highest in the early morning and declining in the late afternoon;<sup>5</sup> however, the normal diurnal variation of circulating testosterone concentrations present in younger men becomes blunted in older men.<sup>11,12</sup>

Serum testosterone concentration assessments can differ by laboratory and timing of blood sample collection; thus, normal values often are reported as ranges and may differ among the various sources. The Endocrine Society Guidelines suggest the lower limit of normal as 280 or 300 ng/dL or the lower limit of normal established by clinicians' local laboratories, but also note that some experts favor a lower threshold than this for judging when replacement therapy is indicated.<sup>1</sup>

Of the total serum testosterone in men, approximately 40% to 50% is bound with a high affinity to sex hormone-binding globulin (SHBG) and is not readily available for use in target tissues.<sup>4,18-20</sup> Approximately 50% to 60% is loosely bound to albumin, 1% to 4% is bound to cortisol-binding globulin, and 1% to 4% is unbound or "free" testosterone.<sup>4,18-20</sup> Free testosterone and testosterone bound to albumin are considered "bioavailable testosterone."<sup>20</sup>

Normal ranges for testosterone are developed using the 95% distribution of testosterone laboratory values for young, healthy adult males with the lower and upper 2.5% of values falling below and above the lower limit of normal and upper limit of normal, respectively.

The normal range for testosterone varies from lab to lab based on assay methodology used and population used to establish the normal range. Although the most commonly cited normal range is 300 to 1,000 ng/dL, many different normal ranges exist with lower limits of 132 ng/dL and upper limits as high as 1,510 ng/dL cited in one study.<sup>21</sup>

The variability in assay methodology and normal range creation and the lack of age-specific normal ranges all create confusion during the work-up and management of potentially hypogonadal men. The ongoing CDC/Manufacturer Hormone Standardization program will help to standardize the way testosterone is analyzed and interpreted.<sup>22</sup>

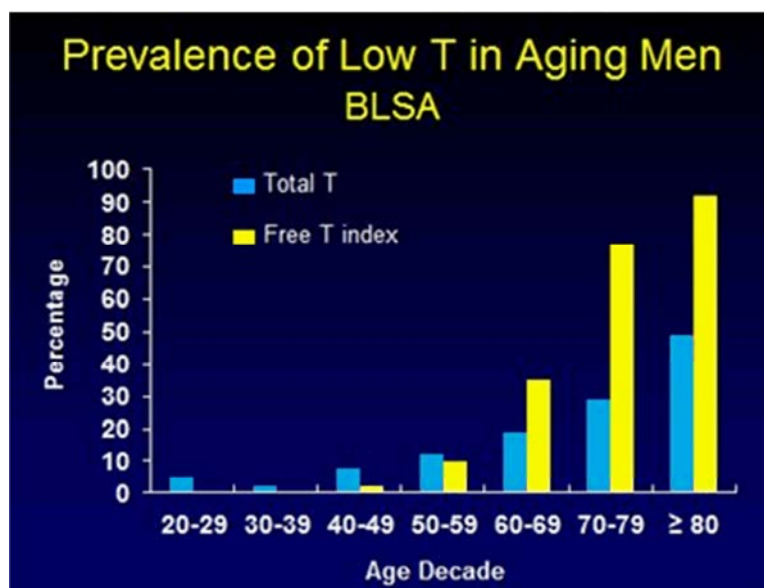
Accurately measuring and interpreting bioavailable and free testosterone poses greater challenges due to the sophistication of the assay technique for accurate assessment (equilibrium dialysis for free testosterone). Fortunately, calculations using SHBG, total testosterone, and albumin allow for an assessment of free and bioavailable testosterone that correlate well with directly measured free and bioavailable testosterone.<sup>23</sup>

The normal range for free testosterone is commonly cited as 5 to 9 pg/mL,<sup>1</sup> while the lower limit of normal for bioavailable testosterone is < 72 ng/dL by one source.<sup>24</sup>

Total and free testosterone fall at a rate of approximately 0.5% and 1.2% per year in men, respectively.<sup>25</sup> The more rapid fall in free testosterone is due to a number of factors, including increases in SHBG that occur with aging (Figure 1).<sup>26</sup> The decline in testosterone observed as men age may not be pathologic in many cases (e.g., not associated with signs and symptoms of hypogonadism). However, the prevalence of symptomatic hypogonadism increases significantly with age.<sup>27</sup> In the Massachusetts Male Aging Study (MMAS), age-specific crude prevalence rates at baseline were 4.1%, 4.5%, and 9.4% for men in their 40s, 50s, and 60s, respectively.<sup>27</sup> Subsequent values at

follow-up were 7.1%, 11.5%, and 22.8% for men in their late 40 to 50s, 60s, and 70s, respectively.<sup>27</sup>

**Figure 1. Prevalence of Low Testosterone in Aging Men**



Source: Harman et al, 2001<sup>26</sup>

## 3.2 Hypogonadism

Hypogonadism is a recognized clinical condition characterized by low concentrations of serum testosterone in association with symptoms such as decreased libido, erectile dysfunction, reduced bone density, reduced lean body mass, depression, and anemia.<sup>28</sup>

### 3.2.1 Classification, Signs, and Symptoms of Hypogonadism

Hypogonadism may be classified as primary (due to testicular failure), secondary (due to insufficient testicular stimulation by pituitary gonadotropins), or combined primary and secondary hypogonadism (Table 2).<sup>1,8,29</sup> In primary hypogonadism, there is a deficiency in testosterone and sperm production.<sup>6</sup> Negative feedback by testicular products (e.g., testosterone, inhibin) on the hypothalamus and pituitary is lost.<sup>6</sup> Basal serum LH

and FSH concentrations are elevated or, despite normal basal gonadotropin concentrations, there is an exaggerated gonadotropin response to LHRH.<sup>6</sup> Many causes of primary hypogonadism have been identified; these causes include Klinefelter syndrome (or other chromosomal disorders), anorchia, Leydig cell hypoplasia, or acquired disturbances of testicular function (e.g., infection, radiation, surgical orchiectomy for testicular cancer).<sup>8,29</sup> Secondary hypogonadism is characterized by a deficiency in testosterone and insufficient production of pituitary gonadotropins, due either to pituitary failure or hypothalamic defects (e.g., diminished/absent GnRH secretion), with apparently normal testicular function.<sup>6,29</sup>

Examples of conditions resulting in secondary hypogonadism include LH or FSH deficiency, severe systemic illness, uremia, and hemochromatosis (Table 2).<sup>8</sup> Other causes of secondary hypogonadism include granulomatous disease, vasculitis, infarction, Kallman syndrome, Prader-Willi syndrome, diabetes, chronic opiate use, and gross obesity.<sup>8</sup>

Combined primary and secondary hypogonadism results from dysfunction in both the testes and hypothalamic-pituitary axis.<sup>1,8</sup> Examples of conditions resulting in combined primary and secondary hypogonadism include hepatic cirrhosis, sickle cell disease, and aging in some instances.<sup>1,8</sup>

**Table 2. Classification of Male Hypogonadism**

<b>Examples of Primary Hypogonadism</b>	
Klinefelter syndrome	Persistent mullerian duct syndrome
XX males; XY/XO mixed gonadal dysgenesis; XYY syndrome	Male pseudohermaphroditism involving androgen receptor defects
Ullrich-Noonan syndrome	Testicular feminization
Myotonic dystrophy (myotonia dystrophica)	Reifenstein syndrome
Sertoli-cell-only syndrome	Infertility due to a receptor defect
Leydig cell hypoplasia	Cryptorchidism
Anorchia	Leprosy
Functional prepubertal castrate syndrome	Acquired disturbances of testicular function (e.g., after testicular trauma, infection, irradiation, chemotherapy)
Enzymatic defects involving testosterone biosynthesis	Autoimmune testicular failure
5 $\alpha$ -reductase deficiency	
Luteinizing hormone/gonadotropin-resistant testis	
<b>Examples of Secondary Hypogonadism</b>	
Hypogonadotropic hypogonadism	Granulomatous disease
Isolated luteinizing hormone or follicle-stimulating hormone deficiency	Vasculitis
Acquired gonadotropin deficiencies	Infarction
Prolactin-secreting pituitary tumors	Kallman syndrome
Severe systemic illness (e.g., chronic kidney disease, HIV, diabetes, alcoholism)	Praeder-Willi syndrome
Uremia	Gross obesity
Hemochromatosis	Secondary to drug therapy (e.g., chronic corticosteroids; chronic opioids, general anesthesia [temporary])
<b>Examples of Combined Primary and Secondary Hypogonadism</b>	
Aging	
Hepatic cirrhosis	
Sickle cell disease	

HIV = human immunodeficiency virus.

Derived from Endocrine Society 2010,<sup>1</sup> Plymate 1994,<sup>8</sup> and Jockenhovel 2004<sup>29</sup>

The Endocrine Society Guidelines<sup>1</sup> list the following signs and symptoms suggestive of testosterone deficiency:

<b>Signs and symptoms suggestive of testosterone deficiency</b>	<b>Signs and symptoms associated with testosterone deficiency, but less specific than those listed in the left column</b>
Incomplete sexual development, eunuchoidism, aspermia	Decreased energy, motivation, initiative, aggressiveness, self confidence
Reduced sexual desire (libido) and activity	Feeling sad or blue, depressed mood, dysthymia
Decreased spontaneous erections	Poor concentration and memory
Breast discomfort, gynecomastia	Sleep disturbance, increased sleepiness
Loss of body (axillary and pubic) hair, reduced shaving	Mild anemia (normochromic, normocytic, in the female range)
Very small or shrinking testes (especially < 5 mL)	Increased body fat, body mass index
Inability to father children, low or zero sperm counts	Diminished physical or work performance
Height loss, low trauma fracture, low bone mineral density	
Reduced muscle bulk and strength	
Hot flushes, sweats	

### 3.2.2 Prevalence of Hypogonadism

Hypogonadism incidence data are difficult to obtain due to the differing ages of hypogonadal onset and diagnosis, and estimating the prevalence of hypogonadism in general is complicated by the various causative (in some cases acquired) factors identified.

Crude and age-specific prevalences of symptomatic androgen deficiency (as defined below) were reported in a randomly sampled population cohort of the MMAS.<sup>27</sup> In this study, androgen deficiency was defined as at least 3 signs and symptoms characteristic of androgen deficiency plus a low total testosterone concentration (< 200 ng/dL) or a total testosterone concentration between 200 ng/dL and 400 ng/dL with free testosterone < 8.9 ng/dL.<sup>27</sup> In 1,691 men at baseline and in 1,087 men at follow-up over a 7- to 10-year period, the crude prevalence rates of androgen deficiency were 6.0% and 12.3%, respectively.<sup>27</sup>

The authors acknowledge that their estimates are conservative and, thus, may underestimate the true prevalence. Notably, 37% to 47% of subjects with total testosterone concentrations < 200 ng/dL at baseline and follow-up recorded fewer than 3 symptoms, which was required for a diagnosis of androgen deficiency in the MMAS Study; however, such a low serum testosterone concentration strongly suggests androgen deficiency.<sup>30</sup>

Other studies in the literature offer a range of estimates of hypogonadism prevalence, which is accounted for by the hypogonadism definition used and the cohort sampling methodology.<sup>27-33</sup> Symptomatic androgen deficiency prevalence rates range from 2.1% to 25.5%. The wide variations in the estimation of prevalence may reflect differences in age ranges, patient characteristics and/or definitions ([Table 3](#)).



**Table 3. Estimation of Prevalence of Testosterone Deficiency**

Study	Design	Results
Massachusetts Male Aging Study (MMAS, 2004)	<ul style="list-style-type: none"> <li>10 year, observational cohort study of men (N = 1,709), age 40 to 70 years</li> <li>•Symptomatic androgen deficiency: at least 3 signs/symptoms<sup>a</sup> and               <ol style="list-style-type: none"> <li>1) TT &lt; 200 ng/dL or</li> <li>2) TT = 200 to 400 ng/dL and calculated FT &lt; 8.91 ng/dL</li> </ol> </li> </ul>	<ul style="list-style-type: none"> <li>Crude prevalence: 6.0% at baseline</li> <li>Doubled to 12.3% at follow-up (average follow-up interval, 8.8 years)</li> <li>Overall, prevalence increased with age</li> <li>Age-specific crude prevalence rates at baseline were 4.1%, 4.5%, and 9.4% for men in their 40s, 50s, and 60s, respectively</li> <li>Subsequent values at follow-up were 7.1%, 11.5%, and 22.8% for men in their late 40 to 50s, 60s, and 70s, respectively</li> </ul>
European Male Aging Study (EMAS, 2010)	<ul style="list-style-type: none"> <li>Survey of a random sample of 8 European centers</li> <li>Men aged 40 – 79 years (N = 3,219)</li> <li>Late onset hypogonadism defined as presence of 3 sexual symptoms and TT &lt; 320 ng/dL and FT &lt; 6.4 ng/dL</li> </ul>	<ul style="list-style-type: none"> <li>Overall prevalence: 2.1%</li> <li>Prevalence increased with age:               <ul style="list-style-type: none"> <li>o 0.1% for 40 – 49 years</li> <li>o 0.6% for 50 – 59 years</li> <li>o 3.2% for 60 – 69 years</li> <li>o 5.1% for 70 – 79 years</li> </ul> </li> </ul>
Boston Area Community Health (BACH, 2008)	<ul style="list-style-type: none"> <li>Population-based, observational survey</li> <li>Multi-ethnic men (N = 1,475), age 30 to 79 years (mean 47.3 ± 12.5 years)</li> <li>Symptomatic androgen deficiency: Symptomatic<sup>b</sup> men with TT &lt; 300 ng/dL and FT &lt; 5 ng/dL</li> </ul>	<ul style="list-style-type: none"> <li>Crude prevalence: 5.6% (CI: 3.6%, 8.6%)</li> <li>Increased with age to 18.4% in the oldest age group (&gt; 70 years old)</li> </ul>

See notes at end of table.

**Table 3. Estimation of Prevalence of Testosterone Deficiency (Continued)**

Study	Design	Results
Hypogonadism In Males (HIM, 2006)	<ul style="list-style-type: none"> <li>Men 45 years old visiting primary care practices in the US (N = 2,165)</li> <li>Hypogonadism: TT &lt; 300 ng/dL or hypogonadism previously diagnosed receiving androgen treatment, regardless of measured TT</li> </ul>	<ul style="list-style-type: none"> <li>Crude prevalence: 38.7% (95% CI: 36.6%, 40.7%)</li> <li>Symptomatic hypogonadism prevalence: 25.5%</li> <li>Risk of hypogonadism increased by 17% for every 10-year increase in age</li> </ul>

CI = confidence interval; FT = free testosterone; N = number of subjects; TT = total testosterone; US = United States

- a Loss of libido, erectile dysfunction, depression, lethargy, inability to concentrate, sleep disturbance, irritability, depressed mood.
- b Having 1 specific symptom (low libido, erectile dysfunction, or osteoporosis) or > 2 nonspecific symptoms (sleep disturbance, depressed mood, lethargy, or low physical performance).

In the Boston Area Community Health (BACH) Survey, 5.6% of men 30 to 79 years of age had symptomatic androgen deficiency (defined as total testosterone < 300 ng/dL and free testosterone < 5 ng/dL plus presence of low libido, erectile dysfunction, osteoporosis or fracture, or two or more of following symptoms: sleep disturbance, depressed mood, lethargy, or diminished physical performance). Prevalence increased with age from 3.1% to 7.0% in men less than 70 years to 18.4% among 70 year olds. Based on testosterone levels alone, 24% of the subjects had total testosterone < 300 ng/dL.<sup>31</sup> When considering the sample of symptomatic testosterone deficient men, 87.8% in the cohort remained untreated with testosterone. The authors speculate that the potential reasons for the above observation was that the condition goes unrecognized or an unwillingness of prescribers to offer testosterone replacement.

### 3.2.3 Comorbid Conditions

Hypogonadism in men is strongly associated with a number of comorbid diseases and conditions. In observational studies, hypogonadal concentrations of endogenous testosterone have been correlated with the following:

Diabetes mellitus,<sup>34-42</sup> obesity,<sup>41,43</sup> insulin resistance,<sup>44-47</sup> abdominal adiposity,<sup>48,49</sup> and metabolic syndrome<sup>50</sup>

Dyslipidemia<sup>36</sup> and CV disease<sup>51-53</sup>

Musculoskeletal disorders such as osteoporosis and osteopenia,<sup>54,55</sup> sarcopenia,<sup>54,56</sup> and frailty<sup>54,55</sup>

HIV-infection and AIDS, particularly among those who also experience muscle wasting<sup>57-59</sup>

Neuropsychological conditions including depression/mood disorders,<sup>60</sup> Parkinson disease,<sup>61</sup> and Alzheimer disease<sup>62</sup>

Sexual dysfunction<sup>63,64</sup>

Chronic pain with chronic opioid use<sup>1</sup>

Although hypogonadism is clearly related to these comorbid conditions, the exact nature of the relationship is not known and it is difficult to determine cause and effect.

Hypogonadism has a complex pathogenesis and the consequences and causes of hypogonadism may affect and be affected by multiple organ systems.<sup>65-68</sup> Many comorbidities, including CVD, become more prevalent with age and may occur in older men with testosterone deficiency simply because of their age.<sup>43,69,70</sup> However, it is clear that hypogonadal men experience a higher risk of these comorbid conditions than eugonadal men of the same age.<sup>71-73</sup>

### 3.2.4 Endocrine Society Guidelines

The Endocrine Society's 2010 Clinical Practice Guidelines for Testosterone Therapy in Men with Androgen Deficiency Syndromes recommends making a diagnosis of androgen deficiency only in men with consistent symptoms and signs (e.g., low libido, increased body fat, muscle wasting, weakness, and osteoporosis) and unequivocally low serum

testosterone level.<sup>1</sup> The Endocrine Society does not recommend screening for androgen deficiency in the general population and recommends that case-finding instruments should not be used to detect androgen deficiency in men receiving health care for unrelated reasons. As outlined in the Guidelines, several disease states have a background rate of hypogonadism that is sufficiently high to warrant assessment of testosterone to screen for hypogonadism. These chronic conditions include sellar disease, treatment with medications such as glucocorticoids or opioids, HIV-associated weight loss, end-stage renal disease or maintenance hemodialysis, moderate to severe chronic obstructive pulmonary disease (COPD), infertility (with assessment of testosterone only as a cause), osteoporosis or low trauma fracture, and type 2 diabetes mellitus (T2DM).<sup>1</sup>

Guidelines suggest that the diagnosis of hypogonadism should be based both on biochemical parameters (e.g., testosterone concentrations) and a thorough evaluation of symptoms.<sup>1,28</sup> Clinicians should obtain an early morning serum testosterone level and if the level is less than the lower limit of normal, commonly cited as 300 ng/dL, clinicians should obtain a confirmatory level on a different day. If testosterone is confirmed to be < 300 ng/dL or the lower limit of normal for the local laboratory, serum FSH and LH should be measured to differentiate between primary and secondary hypogonadism.<sup>1,28</sup> Once a complete evaluation of the patient's overall clinical picture has ruled out acute illnesses or medications that may be responsible for temporarily low testosterone levels, testosterone replacement may be initiated. The Guidelines also outline appropriate follow-up measures for monitoring testosterone replacement efficacy and safety. According to the Endocrine Society, testosterone therapy is recommended in men with symptomatic androgen deficiency to induce and maintain secondary sexual characteristics and to improve sexual function, sense of well-being, muscle mass and strength, and bone mineral density.

### **3.3 Testosterone Replacement Therapy**

#### **3.3.1 Introduction**

The goal of treating men with symptomatic low testosterone is to both increase the serum testosterone concentration to within the normal physiological range and to resolve the symptoms of hypogonadism.<sup>1</sup> The focus of this section will be to summarize the evidence of benefit of TRT for treating common signs and symptoms associated with hypogonadism.

This document uses the term "testosterone replacement therapy." The authors recognize that some published studies included men with normal and low-normal baseline testosterone levels (i.e., testosterone use as supplementation rather than replacement therapy) in addition to or rather than hypogonadal men. However, the TRT Sponsors recognize that the only FDA-approved indication for testosterone is in adult males with an absence or deficiency in circulating testosterone.

#### **3.3.2 Limitations of Literature Evaluating Benefits of Testosterone Replacement Therapy**

There are limitations in testosterone-related research that include, but are not limited to:

- Most studies include fewer than 100 participants.

- Variable selection criteria (e.g., in many studies, the selection of men was not based on having required abnormalities, such as sexual dysfunction, but were assessed for that endpoint).

- Variable definitions of "hypogonadism" or "relative hypogonadism" (some studies included men with normal testosterone levels).

- Differences in dose and duration of testosterone therapy.

- Different methodologies used to assess study endpoints.

- Relative lack of FDA-validated outcome instruments (e.g., sexual dysfunction, fatigue).

- Preexisting comorbidities of different patient populations studied.

In addition, a publication bias against negative or equivocal studies may limit a complete compilation of studies. Studies on testosterone deficiency and hypogonadism continue to evolve and research is ongoing. No large placebo-controlled outcome studies have been conducted to date for TRT benefit (e.g., fracture risk, fall prevention, long-term effects on decreasing depression).

### **3.4 Effects of Testosterone Replacement in Hypogonadal Men**

The focus of this section is to summarize the evidence of benefit of TRT for treating common signs and symptoms associated with hypogonadism. A literature review of the evidence for benefit of TRT was performed by searching PubMed for the terms "hypogonadism" and "testosterone replacement." Studies of short-term therapy and PK studies were not reviewed. In addition, articles not identified through the specified search, but were relevant, were reviewed when identified through indirect sources. The next subsections cover key data for the benefits of TRT on several target organ systems.

In total, more than 200 studies were identified that examined a variety of endpoints. Of the above studies, more than 80 studies were placebo-controlled and of these, 22 included 100 total participants. Eighty-four studies included 30 participants irrespective of study design.

Studies with testosterone-related endpoints, such as bone mineral density, fat mass, lean mass, sexual function, fatigue, and mood are summarized below. Additionally, 2 comorbidities that are associated with a higher prevalence of hypogonadism (i.e., diabetes and HIV) are covered. Although this section covers the most commonly studied endpoints for testosterone replacement-related research, it is not a comprehensive list of endpoints assessed. Additional information may be found in recently published comprehensive reviews and guidelines.<sup>74-83</sup>

### 3.4.1 Benefits Related to Lean Mass, Muscle Strength, and Fat Mass

Many studies have investigated the effects of TRT on fat mass and lean mass in the same studies and these results will be discussed together. Several randomized trials of testosterone administration reported increases in lean mass (both whole-body and appendicular) and muscle strength, along with decreases in fat mass.<sup>4,49,84-98</sup> Body composition changes were more consistently observed in studies with TRT duration longer than 3 months.<sup>91</sup>

**Hildreth et al** (2013)<sup>99</sup> found that healthy community dwelling older men (mean age,  $66 \pm 5$  years) assigned to resistance training plus testosterone showed a 1.2 kg greater decrement in fat mass and a 1.7 kg greater increase in lean mass compared with men randomized to placebo. The study also showed improvements in fat mass, lean mass, and upper body strength in the group assigned to testosterone without resistance training versus placebo-treated men who did not undergo resistance training, potentially representing benefits in patient populations where successful lifestyle interventions are not implemented.<sup>99</sup>

In a meta-analysis of 16 studies, **Isidori et al** (2005)<sup>76</sup> showed an average reduction of 6.2% in total body fat with testosterone treatment averaging 9 months. Similarly, in an open-label registry cohort of obese men given intramuscular testosterone, body weight, waist circumference, and body mass index (BMI) decreased in a linear manner over a 5-year treatment period.<sup>100,101</sup>

**Spitzer et al** (2013)<sup>102</sup> characterized the benefits of testosterone on physical function, mobility, and frailty. They found that, compared with men with normal testosterone levels, those with low testosterone had worse physical performance,<sup>103-105</sup> decreased mobility, increased frailty, and an increase in the number of falls.<sup>106,107</sup> Several studies reported that the effect of testosterone on muscle mass and strength is dose-related.<sup>84,98,108,109</sup>

Testosterone administration has also been associated with an improvement in physical function and stair climbing.<sup>88,109</sup> **Bhasin et al** (2005)<sup>110</sup> showed that the skeletal muscles of older men are as responsive to testosterone as those of young men.

Both seated bench press and controlled leg extension, using a one-repetition maximum weight, have been measured in testosterone replacement studies and act as surrogates for important activities of daily living, such as stair climbing and walking.<sup>94,111,112</sup> These assessments measure the maximal force-generating capacity of the muscles used to perform the tests (e.g., legs, arms/chest).<sup>113</sup>

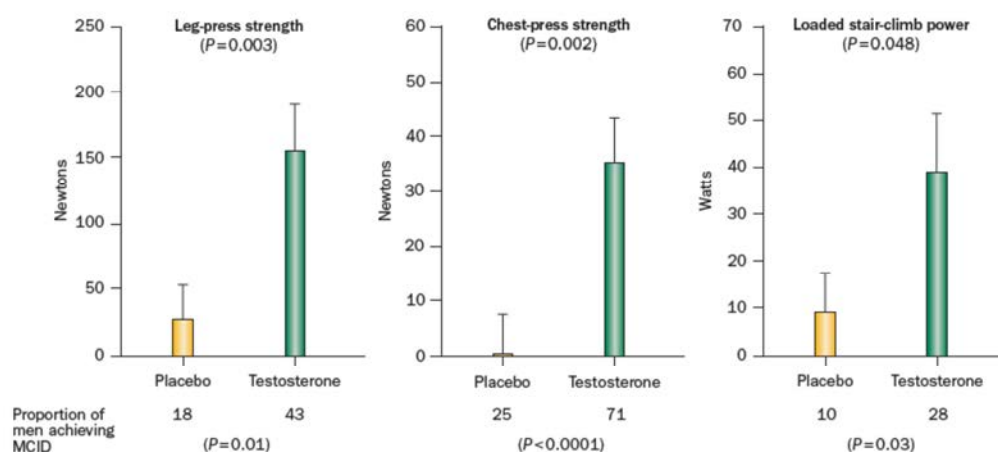
**Srinivas-Shankar et al** (2010)<sup>114</sup> and **Basaria et al** (2010)<sup>115</sup> performed 6-month randomized, placebo-controlled trials of testosterone treatment in men with mobility limitations. Collectively, they found that treatment with testosterone gel was associated with greater improvements in isometric knee extension peak torque, lean body mass, and fat mass, along with significant improvements in leg-press strength, chest-press strength, and stair-climbing power for men who received testosterone compared with men who received placebo (**Figure 2**).<sup>114</sup> Physical function did not differ significantly between treatment groups, but improved among patients who were older and frailer.<sup>114</sup> These results support similar studies demonstrating significant increases in muscle strength relative to placebo.<sup>94,96</sup>

Studies do not always find a separation from placebo in changes in muscle strength.<sup>57</sup> **Nair et al** (2006)<sup>116</sup> found a small but significant increase in lean mass in men receiving low-dose TRT (transdermal testosterone patch, 5 mg/day), the investigators did not believe this represented a significant clinical effect since it was not associated with a significant increase in the thigh-muscle area or with an improvement in any of the performance measures.<sup>116</sup>

Overall, increases in lean mass and decreases in fat mass are consistently observed in TRT studies. Changes in muscle strength and physical function have also been observed less consistently.



**Figure 2. Effects of Testosterone Replacement Therapy on Strength in the Leg-Press and Chest-Press Exercises and on Loaded Stair-Climbing Power in the Testosterone in Older Men (TOM) Trial**



MCID = minimal clinically important difference

Source: Spitzer et al, 2013<sup>102</sup>

**Table 4. Strengths and Limitations of Changes in Fat Mass, Lean Mass, and Muscle Strength**

Strengths	Limitations
<ul style="list-style-type: none"> <li>Objective metric (e.g., via DEXA)</li> <li>Lean mass and fat mass consistently improve across numerous TRT studies of differing duration and design</li> <li>Appears to be a good dose/response relationship for fat mass and lean mass</li> <li>Biologically consistent findings of testosterone withdrawal and replacement studies for muscle strength</li> <li>Number of studies that assessed lean mass and fat mass</li> </ul>	<ul style="list-style-type: none"> <li>Unclear what the long-term benefits are for the changes seen in fat mass and lean mass</li> <li>Visceral adiposity has not been shown to consistently decrease with TRT</li> <li>Many studies recruited men who had normal testosterone levels and no physical dysfunction at baseline; further increases in performance is unexpected in these men</li> <li>Muscle mass and strength may increase with testosterone therapy, but the benefits on clinically important health outcomes have not been shown (falls, fractures and disability)</li> <li>Muscle strength may not always represent improved functional capacity</li> </ul>

DEXA = dual-energy x-ray; TRT = testosterone replacement therapy

Limitations for findings regarding muscle strength were adapted from Spitzer et al<sup>102</sup>

### 3.4.2 Benefits Related to Bone Mineral Density and Bone Architecture

In men, 30% to 60% of osteoporosis cases occur due to secondary causes, among which hypogonadism is the most common.<sup>117</sup> Hypogonadal men show decreases in trabecular bone and BMD compared with age-matched eugonadal men.<sup>54,118</sup> Typically, BMD is 9% to 17% lower in hypogonadal versus eugonadal men,<sup>54</sup> and some epidemiologic studies show that low testosterone levels are associated with increased fracture risk.<sup>119</sup>

A number of clinical trials have demonstrated that BMD increased significantly, in some cases to near normal levels, with TRT in hypogonadal men.<sup>120-123</sup> As shown in Figure 3, in several randomized, double-blind, placebo-controlled trials, TRT significantly increased BMD in hypogonadal men.<sup>88,94,124-126</sup> Because increases in BMD in hypogonadal men receiving placebo or no replacement therapy would be unexpected, the above treatment effects suggest that these results are due to testosterone versus a placebo effect or a disease that waxes and wanes.

**Benito et al** (2005)<sup>54</sup> examined TRT over a 2-year period in 10 severely hypogonadal men. In addition to a 7.4% and 3.8% increase in spine and total hip bone mineral density, respectively, the authors observed an 11% increase and 7.5% decrease in the surface-to-curve ratio and topological erosion index, respectively, via micro-MRI measurement. More recent studies have confirmed these micro-MRI findings.<sup>127</sup> These changes show that the increases in bone mineral density observed with TRT are accompanied by beneficial changes in bone architecture.

**Aversa et al** (2012)<sup>128</sup> looked at the effects of 36 months of TRT in a cohort of men (mean age 57 years) with metabolic syndrome and baseline testosterone levels < 320 ng/dL (mean testosterone at baseline; 240 ng/dL). Despite modestly low baseline testosterone levels and participants who were, on average, in their mid-50s, participants had mild osteopenia prior to starting TRT and gained approximately 5% lumbar and femoral bone mineral density per year during the study. The above baseline characteristics appear to be consistent with the demography of current users reported in

medical claims and prescription databases (e.g., largest numbers of prescriptions written for men in their late 40s to early 60s; mean testosterone levels of approximately 250 ng/dL and commonly observed comorbid conditions such as hypertension, hyperlipidemia. See Section 5.0 for further discussion. Therefore, it is not unreasonable to assume that men with these baseline characteristics 1) have some level of target organ detriment due to relative hypogonadism, and 2) progressive beneficial changes in bone density are observed over time following TRT.

**Figure 3. Effects of Testosterone on Bone Density Measured as Mean Difference on Absolute Values (Panel A) and Reported as Percentage Change from Baseline at Lumbar Spine (Panel B)**

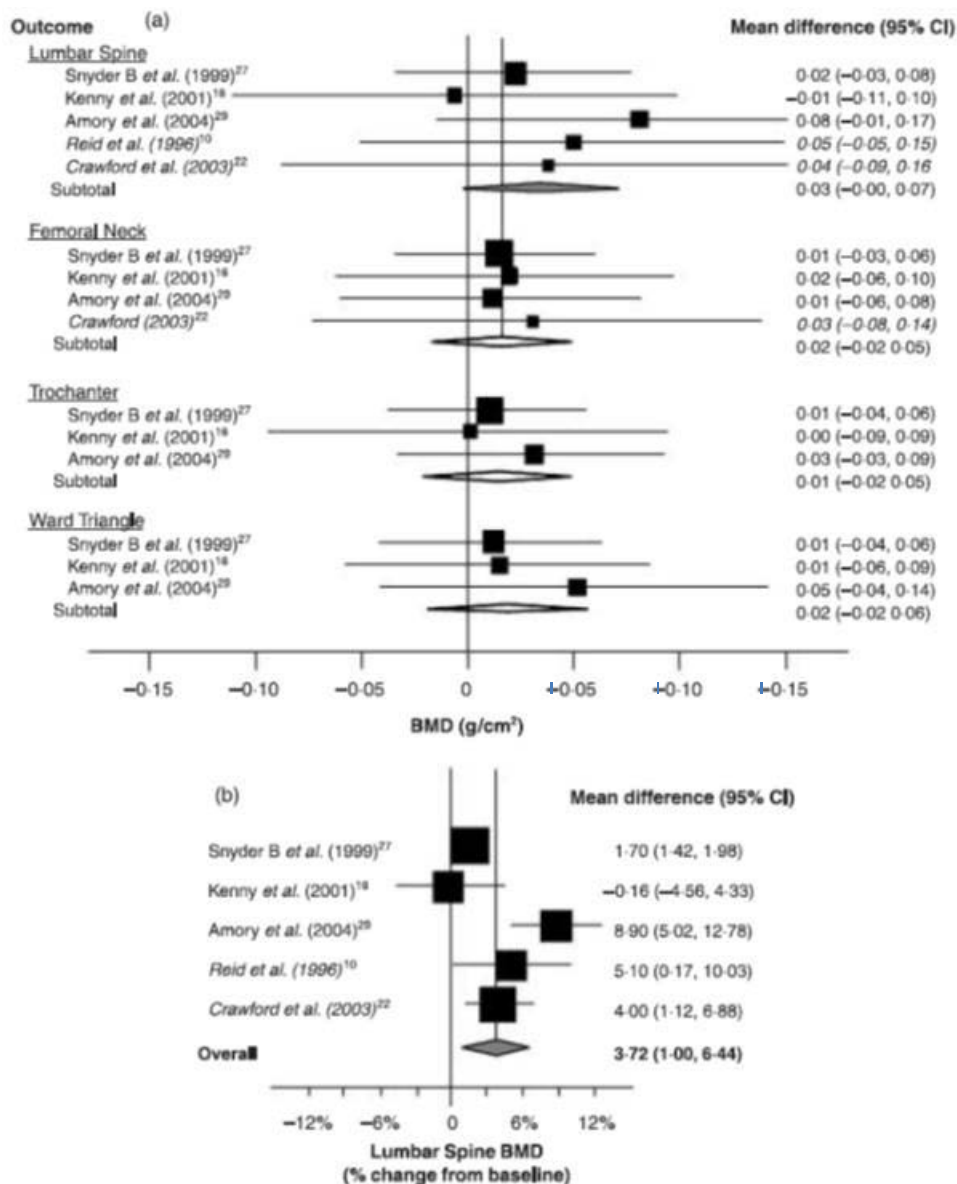


Figure and caption are from Isidori et al,<sup>76</sup> based on data from Snyder et al,<sup>120</sup> Kenny et al,<sup>94</sup> Amory et al,<sup>124</sup> Reid et al,<sup>125</sup> and Crawford et al<sup>126</sup>

Overall, data support rather consistent positive changes in BMD in a variety of study designs and patient populations. Though parameters of bone quality have only been studied more recently, bone architecture also appears to be beneficially impacted.

**Table 5. Strengths and Limitations of Changes in Bone Mineral Density**

Strengths	Limitations
<ul style="list-style-type: none"> <li>Objective metric (e.g., DEXA assessment)</li> <li>Changes in bone density seen with TRT are consistent with those seen with estrogen replacement in women</li> <li>Increases in bone density are accompanied by beneficial modifications of bone architecture</li> <li>Number of studies that studied bone density</li> </ul>	<ul style="list-style-type: none"> <li>Absence of fracture data</li> <li>Fractures occur less often in men versus women; fragility fractures occur in older men</li> <li>The magnitude of benefit appears to be related to baseline bone density and serum testosterone</li> <li>Lower doses of TRT do not always impact bone density</li> </ul>

DEXA = dual-energy x-ray; TRT = testosterone replacement therapy

### 3.4.3 Benefits Related to Sexual Function

Sexual dysfunction (e.g., loss of libido) is a common symptom of hypogonadism.<sup>1,77,129</sup> Complaints related to sexual function (i.e., erectile dysfunction and decreased sexual desire) are one of the most common presenting symptoms for hypogonadal men.<sup>130,131</sup> Aspects of arousal that are not linked to strong visual stimuli, such as nighttime tumescence and self-reported measures of libido, are reduced in hypogonadal men, and these measures of sexual function improve following initiation of androgen therapy.<sup>132</sup> Accordingly, sexual function has been assessed using various questionnaires (International Index of Erectile Function [IIEF], UCLA 7-day psychosexual questionnaire) in double-blind studies of testosterone treatment in hypogonadal men,<sup>17,133-137</sup> The improvements in sexual function observed in these trials correlated with serum testosterone concentrations achieved with therapy.<sup>138,139</sup>

**Corona et al** (2014)<sup>78</sup> recently published a meta-analysis on the effects of testosterone replacement/supplementation and sexual function and showed that in men with baseline testosterone levels below 12 nmol/L, TRT improved the number of nocturnal erections, sexual thoughts and motivation, number of successful intercours, scores of erectile

function, and overall sexual satisfaction, while no benefit was noted in men with baseline testosterone levels > 12 nmol/L.<sup>78</sup> The systematic review showed that 11 of the 20 studies reported a significant improvement in at least one measure of erectile function in the TRT group versus the placebo group. The authors found significant testosterone benefits versus placebo for both erectile function and sexual desire or libido (Table 5), despite some individual studies in the literature suggesting testosterone benefit is limited to sexual desire.<sup>140,141</sup>

The total number of men pooled in the above analysis was 1,152 and 952 men randomized to testosterone and placebo, respectively. The analysis also examined 494 and 479 additional men randomized to testosterone and placebo, respectively, who participated in studies where the effect of testosterone was evaluated with phosphodiesterase type 5 inhibitors (PDE5i).

**Table 6. Mean ± SD Difference on Total and Domain Score of the International Index of Erectile Function (IIEF-15) Between the Testosterone and Placebo Groups**

IIEF-15 Domains	Mean Differences (95% CI)	P Value
Erectile Function	3.726 (1.621; 5.830)	0.001
Sexual Desire	0.285 (0.091; 0.479)	0.004
Orgasmic Function	1.620 (0.000; 3.229)	0.05
Intercourse Sexual Satisfaction	1.503 (0.265; 2.740)	0.017
Overall Satisfaction	0.060 (−0.517; 0.638)	0.838
Total IIEF-15	7.282 (2.914; 11.650)	0.001

CI = confidence interval; IIEF = International Index of Erectile Function

Reproduced from Corona et al<sup>78</sup>; erectile function domain max score = 30; sexual desire max score = 10; orgasmic function max score = 10; intercourse sexual satisfaction max score = 15; Total IIEF-15 max score = 75

Since the issuance of the 2009 FDA *Final Guidance on Patient-Reported Outcomes Measures: Use in Medical Product Development to Support Labeling Claims*,<sup>142</sup> TRT Sponsors have supported the development of FDA-validated questionnaires to assess the change in hypogonadal symptoms noted with testosterone replacement across a number of domains including but not limited to sexual function (The Sexual Arousal, Interest and

Drive [SAID] Scale, Lilly; Hypogonadal Impact of Symptoms Questionnaire [HIS-Q], AbbVie Inc.). An ongoing study of testosterone solution versus placebo with over 600 hypogonadal men assesses the impact of testosterone on sex drive in hypogonadal men using the SAID Scale (NCT01816295), as well as the impact of testosterone on energy in hypogonadal men using a disease-specific assessment, the Hypogonadism Energy Diary (HED). The study is scheduled to be completed during the last quarter of 2014, and results will be available in 2015.

Overall, data support sexual complaints as being one of the most common reasons hypogonadal men seek further evaluation. Data suggest that sexual desire and, to a lesser consistent extent, erectile function are responsive to testosterone in hypogonadal men. Heterogeneity in the patient populations studied make interpretation of the sexual function benefits difficult in some instances (Table 7).

**Table 7. Strengths and Limitations of Changes in Sexual Function**

Strengths	Limitations
<ul style="list-style-type: none"><li>• Number of studies where erectile function, sexual desire have been examined</li><li>• Number of conditions/comorbidities where the endpoint has been examined</li><li>• Appears to be one of the most common presenting complaints for men with hypogonadism</li><li>• Improvement shown across a variety of outcome tools (e.g., IIEF, Wang UCLA 7-day psychosexual questionnaire, Aging Male Symptoms [AMS] scale)</li></ul>	<ul style="list-style-type: none"><li>• Numerous studies enrolling men with testosterone levels in the low-normal range</li><li>• Endpoint often assessed in studies even if participants are not required to have problems with sexual function at baseline</li><li>• Inconsistent results regarding durability of effect</li><li>• Currently no available FDA-validated patient-reported outcome available</li><li>• Placebo-effect; placebo-controlled studies show some level of improvement with placebo</li></ul>

AMS = Aging Males' Symptoms; FDA = Food and Drug Administration; IIEF = International Index of Erectile Function; UCLA = University of California, Los Angeles

### 3.4.4 Benefits Related to Fatigue

Gelhorn et al<sup>131</sup> showed that fatigue was one of the 4 most common chief complaints, following low sexual desire, erectile dysfunction, and feeling tired, for participants who sought testosterone replacement during qualitative research focus groups while creating the HIS-Q.<sup>131</sup> Another recently published study surveying 133 hypogonadal men in 2012

showed that fatigue was the second most common cause for hypogonadal men to seek testosterone replacement following erectile dysfunction.<sup>130</sup>

Improvement in fatigue and increased vigor were observed in a placebo-controlled trial of testosterone therapy in hypogonadal men using simple scales to assess fatigue.<sup>133</sup> A double-blind, placebo-controlled study assessing the effects of TRT in 29 men with advanced cancer showed that testosterone improved fatigue scores (FACIT-fatigue) while the scores for placebo-treated patients regressed, but this difference was not statistically significant. The correlation of FACIT score and increases in testosterone at 1 month was significant ( $r = 0.878$ ;  $P = 0.021$ ).<sup>143</sup> A 6-month observational study (N = 799) noted significant changes from baseline for the overall scores on the Multidimensional Fatigue Inventory (MFI) as well as each subscore (general fatigue, mental fatigue, physical fatigue, reduced motivation, and reduced activity). Although the changes in total scores from baseline were significant for men older and younger than 50 years of age, the mean absolute and relative decrease was significantly greater in younger men.<sup>144</sup> As previously mentioned, ongoing work in this area (e.g., HED) will help characterize the effects of testosterone on fatigue.

Overall, data support complaints related to fatigue as being one of the most common reasons hypogonadal men seek further evaluation. While some studies suggest that testosterone may be beneficial in addressing symptoms of fatigue, this area has not been studied extensively in large well-controlled trials. Heterogeneity of scales and patient populations studied make it difficult to interpret benefits in fatigue (Table 8).



**Table 8. Strengths and Limitations of Changes in Fatigue**

Strengths	Limitations
<ul style="list-style-type: none"> <li>Questions about fatigue, lack of energy and/or tiredness are common components of hypogonadism questionnaires (e.g., AMS, ADAM, HIS-Q), supporting fatigue as a component of the symptom complex typically experienced by hypogonadal men</li> <li>Several plausible mechanisms for androgen deficiency to cause fatigue (e.g., reduced muscle mass, relative anemia, increased fat mass), coupled with the expected changes from replacement therapy</li> </ul>	<ul style="list-style-type: none"> <li>FDA-validated questionnaires specifically assessing fatigue in hypogonadal men do not currently exist</li> <li>Fatigue is a broad term encompassing a variety of meanings to different people</li> <li>Fatigue is a broad concept that has numerous etiologies (e.g., work, stress, sleep, mental fatigue, physical fatigue), many of which may not be related to hypogonadism</li> </ul>

ADAM = Androgen Deficiency in Aging Males; AMS = Aging Males' Symptoms; FDA = Food and Drug Administration; HIS-Q = Hypogonadal Impact of Symptoms Questionnaire

### 3.4.5 Benefits Related to Mood and Cognition

Mood disturbances (e.g., anger and depression) have been observed in hypogonadal men.<sup>1,129,144</sup> Low testosterone concentrations have been reported in men with treatment-refractory depression and in older men with dysthymia.<sup>146,147</sup> In an observational study of 748 men 50 years of age and older who were free of a depressive illness prior to the observation period, men with testosterone levels < 250 ng/dL had a 78% increased relative incidence (18.5% versus 10.4% for men below and above 250 ng/dL, respectively) of depressive illness over the 2-year period.<sup>148</sup>

In the Rancho-Bernando study of 856 older men (59 to 89 years of age), scores on the Beck Depression Inventory (BDI) were significantly and inversely associated with bioavailable testosterone ( $P = 0.007$ ), independent of age, weight change, and physical activity.<sup>149</sup> There was a graded stepwise decrease in bioavailable testosterone with increasing level of depressed mood.<sup>149</sup> Conversely, **Sachar et al** did not observe correlations between endogenous testosterone level and depression.<sup>150</sup>

Numerous studies have reported that TRT improved mood in hypogonadal men,<sup>113,133,144,151-153</sup> although other studies have shown no improvement<sup>17,154-157</sup> or

improvement from baseline without an improvement when compared with placebo.<sup>102,158,159</sup> For example, TRT did not improve mood in eugonadal men with or without sexual dysfunction.<sup>151,160,161</sup> In a 3-year open-label extension portion of a 6-month study, positive mood scores improved significantly compared with baseline, and improvements were sustained ( $P = 0.0022$ ); negative mood scores decreased and remained significantly lower than baseline ( $P = 0.0013$ ).<sup>95,113</sup>

Testosterone replacement therapy has also demonstrated short-term efficacy in augmenting the effect of antidepressants to alleviate treatment-refractory depression in hypogonadal men.<sup>146</sup> Testosterone replacement therapy improved depressive symptoms and quality of life in treatment-resistant, depressed, hypogonadal men.<sup>152,158</sup> Finally, when **Amanatkar et al** (2014)<sup>162</sup> reviewed the effect of TRT on depressive symptoms in a meta-analysis of 944 patients, a significant positive impact of TRT on mood was noted ( $z = 4.592$ ;  $P < 0.0001$ ), with the effect seen specifically in the studies of men younger than 60 years of age.

Overall, studies report mixed results of the effects of TRT on cognition.<sup>79</sup> Some studies have reported cognitive benefit even in men with mild cognitive deficits or memory disorders such as Alzheimer's disease,<sup>163</sup> and TRT has been shown to improve spatial ability,<sup>156</sup> verbal fluency,<sup>164</sup> and working memory<sup>165</sup> in elderly men. However, other studies did not show effects of TRT on cognition.<sup>166-169</sup>

Overall, data support an association between depressive illnesses and hypogonadism and suggest that testosterone may improve mood in symptomatic hypogonadal men. Changes in mood from baseline should be interpreted with caution, given the lack of separation from placebo in a number of studies (Table 9).

**Table 9. Strengths and Limitations of Changes in Mood and Cognition**

Strengths	Limitations
<ul style="list-style-type: none"> <li>• Changes in mood a common, yet nonspecific complaint in men presenting with hypogonadism</li> <li>• Changes in mood can be detected in short-term studies (e.g., 3-month studies)</li> </ul>	<ul style="list-style-type: none"> <li>• A portion of the cognition and mood data comes from men with complicating comorbidities such as depressive disorders and MCI</li> <li>• Mood is beneficially impacted in studies, many of which do not include placebo</li> <li>• Lack of FDA validated scales to assess mood in hypogonadal men</li> <li>• Nonspecific complaint with numerous etiologies</li> <li>• Changes in cognition are sometimes difficult to detect with short-term follow-up</li> </ul>

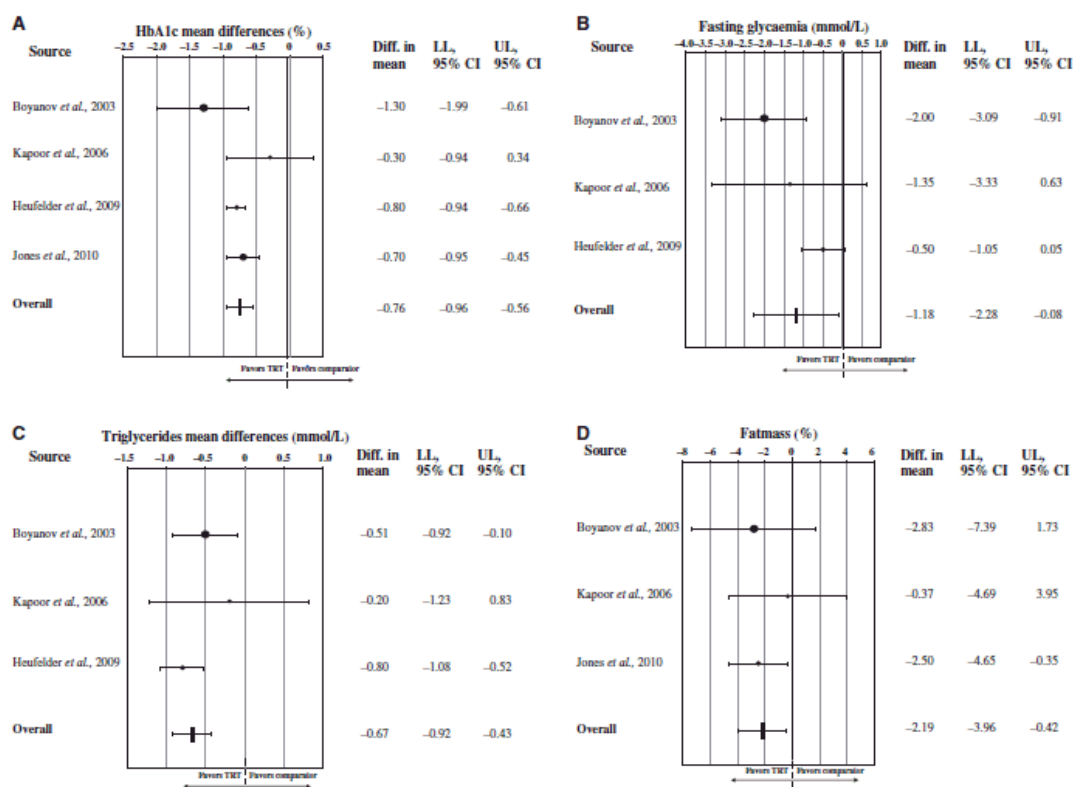
FDA = Food and Drug Administration; MCI = mild cognitive impairment

### 3.4.6 Benefits Related to Special Populations

#### 3.4.6.1 Metabolic Syndrome and Type 2 Diabetes Mellitus

Many studies have demonstrated an association between low testosterone and T2DM.<sup>170,171</sup> Approximately 50% of aging, obese men presenting to diabetes clinics have lowered testosterone levels.<sup>172</sup> In a systematic review of 4 randomized clinical trials of TRT in hypogonadal men with T2DM, **Corona et al** (2011)<sup>171</sup> reported that TRT was associated with significant reductions in fasting plasma glucose, glycosylated hemoglobin (HbA<sub>1c</sub>), fat mass and triglycerides, with no significant difference in total or high-density lipoprotein (HDL) cholesterol, blood pressure, or BMI ([Figure 4](#)). Similarly, in a meta-analysis of 5 randomized controlled trials of men with low testosterone and T2DM, **Cai et al** (2014)<sup>170</sup> reported that TRT reduced fasting plasma glucose, fasting serum insulin, HbA<sub>1c</sub>, and triglyceride levels.

**Figure 4. Weighted Differences of Mean HbA<sub>1c</sub> (Panel A), Fasting Glycemia (Panel B), Triglycerides (Panel C), and Fat Mass (Panel D) Across Randomized Controlled Trials**



CI = confidence interval; HbA<sub>1c</sub> = hemoglobin A<sub>1c</sub>; LL = lower limit; TRT = testosterone replacement therapy; UL = upper limit.

Figure and caption are from Corona *et al.*<sup>171</sup> Data are from Boyanov *et al.*,<sup>173</sup> Kapoor *et al.*,<sup>174</sup> Heufelder *et al.*,<sup>175</sup> and Jones *et al.*<sup>176</sup>

Metabolic syndrome is typically diagnosed based on common clinical measures including waist circumference, triglycerides, HDL cholesterol, blood pressure, and fasting glucose level.<sup>177</sup> A cumulative registry study to evaluate the effects of 5 years of TRT on functional metabolic profiles in 255 hypogonadal males (33 – 69 years), showed significant losses in body weight, waist circumference, and BMI at Year 1 that remained significant at the end of each year compared with the previous year over the 5-year observation period, as well as significant reductions in fasting blood glucose, HbA<sub>1c</sub>, total

cholesterol, low-density lipoprotein (LDL) cholesterol, and C-reactive protein, and an increase in HDL cholesterol.<sup>101</sup>

Betancourt-Albrecht and Cunningham (2003)<sup>69</sup> suggested that the effects of androgen treatment on insulin sensitivity may be caused by the change in body composition and by inhibition of lipoprotein lipase activity, resulting in reduced triglyceride uptake and accelerated triglyceride release from abdominal adipose tissue.

The TRT Sponsors recognize that 1) testosterone is approved for replacement therapy, 2) men with T2DM tend to have low testosterone levels more often than their euglycemic counterparts, but 3) at this time, data do not support the effectiveness of TRT use in hypogonadal or near-hypogonadal men with T2DM as an adjunct to standard antihyperglycemic medications to beneficially impact HbA<sub>1c</sub> and insulin resistance. Consideration of unpublished and more recently published TRT studies in men with low or low-normal baseline testosterone levels appear to demonstrate a reduced treatment effect versus placebo on endpoints such as HbA<sub>1c</sub> and fasting glucose in previous meta-analyses.<sup>178,179</sup>

Overall, data support an association between higher rates of hypogonadism and obesity, diabetes, and insulin resistance. Data suggest that testosterone may improve measures of insulin resistance in hypogonadal men with diabetes and other metabolic derangements. However, optimization of background insulin sensitizers may minimize the beneficial effects of testosterone (Table 10).

**Table 10. Strengths and Limitations of Improvements in Glycemic Control in Metabolic Syndrome and Type 2 Diabetes Mellitus**

Strengths	Limitations
<ul style="list-style-type: none"> <li>There appears to be an association of hypogonadism with insulin resistance, poor glycemic control, visceral adiposity, and hypercholesterolemia</li> <li>Improvement across fasting glucose and HbA<sub>1c</sub> appears is more evident in obese hypogonadal men with metabolic syndrome or T2DM</li> </ul>	<ul style="list-style-type: none"> <li>Some studies do not control background insulin sensitizers</li> <li>Older studies included men with relatively high baseline HbA<sub>1c</sub> levels</li> </ul>

HbA<sub>1c</sub> = hemoglobin A<sub>1c</sub>; T2DM = type 2 diabetes mellitus

### 3.4.6.2 Human Immunodeficiency Virus

The reported prevalence of hypogonadism among men with HIV/AIDS historically has ranged from approximately 25% to 60%, depending on the extent of disease progression.<sup>57-59,180,181</sup> The TRiUS registry reported that 9.7% of the hypogonadal cohort were HIV-positive.<sup>182</sup>

Testosterone replacement therapy has been shown to increase lean body mass,<sup>183-185</sup> decrease insulin resistance,<sup>186</sup> and improve mood and depression in men with HIV infection.<sup>184,187</sup> In a randomized, double blind, placebo-controlled trial of 88 HIV-positive men with abdominal obesity and hypogonadism undergoing TRT, there was a significantly greater decrease in whole body, total, and subcutaneous abdominal fat mass (but not visceral fat) compared with placebo ( $P < 0.001$ ), and an increase in lean body mass compared with placebo ( $P = 0.02$ ).<sup>185</sup> Weight loss also occurs in HIV-infected men who remain eugonadal. Two studies in eugonadal men with HIV-associated weight loss reported that lean body mass was significantly increased and a positive effect of testosterone on muscle attenuation over a 3-month treatment period compared with placebo.<sup>188,189</sup> Similarly, a randomized, placebo-controlled study of 54 eugonadal men with HIV-associated weight loss found that, as HIV treatments have become more effective over time, the prevalence of hypogonadism has decreased accordingly.<sup>190</sup>

Overall, data suggest that testosterone use may be beneficial in HIV-infected men with weight loss (Table 10). Testosterone increases lean mass and promotes weight maintenance in HIV-infected men.

**Table 11. Strengths and Limitations of Testosterone Replacement Therapy in HIV-Infected Males**

<b>Strengths</b>	<b>Limitations</b>
<ul style="list-style-type: none"><li>• Relatively well studied special population</li><li>• Potential for improvement in insulin resistance is promising given the frequency of metabolic complications in HIV infected men</li></ul>	<ul style="list-style-type: none"><li>• Milder manifestations of the HIV/AIDS spectrum may show lesser hypogonadal impairment.</li><li>• Comorbid chronic diseases and opioid use/addiction are frequent confounders in studies characterizing prevalence</li><li>• As HIV therapies continue to improve, the incidence of hypogonadism seems to be decreasing over time</li></ul>

AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus

### **3.4.6.3 Additional Special Populations**

Pilot studies have been conducted to assess the effectiveness of TRT and/or testosterone therapy in a number of other conditions (e.g., Alzheimer's disease, Parkinson's disease, liver transplant) that are beyond the scope of this summary of evidence. Studies in these areas often examine an endpoint directly related to the condition in question with varying degrees of success, along with a number of traditional endpoints seen in TRT studies, such as sexual function.<sup>191-195</sup>

## **3.5 Limitations and Uncertainties for the Evidence of Benefit**

### **3.5.1 Late Onset Hypogonadism (Androgen Deficiency of the Aging Male)**

In 2004, the Institute of Medicine (IOM) published the results of their deliberations on the issue of testosterone replacement in men 65 years of age or older. The IOM recommend conducting more controlled efficacy studies in this population before larger outcomes studies. Although a number of placebo-controlled trials were conducted, many of these

trials were small, with treatment groups of fewer than 10 to 15 patients. For a detailed review of these trials, see **Liverman et al** (2004).<sup>196</sup> Studies that focused on hypogonadal men with no other apparent etiology for low testosterone aside from aging have been conducted since the IOM report. One such study confirmed the beneficial changes in fat mass, lean mass, and bone density following 1 year of testosterone replacement, while showing inconsistent effects on sexual function versus placebo in men with mean baseline total Aging Male Symptoms (AMS) scores indicative of moderate impairment. A subgroup analysis suggested that a stronger improvement in men younger than 60 years of age than in men 60 years of age and older.<sup>197,198</sup>

The ongoing T Trial was designed to characterize the benefits of testosterone use in older men, but will also provide relevant information on safety. The study will also offer insight on the risks of replacement therapy in the above population. The results of the T Trial are expected in the early part of 2015; therefore, this briefing document will not cover in detail the topic of late onset hypogonadism in older men.<sup>199</sup>

### **3.6 Ongoing Studies**

The TRT Sponsors would like to describe a few selected ongoing studies as this space continues to evolve.

The T Trial (sponsored by the NIH/NIA) is a study designed to assess whether testosterone treatment of hypogonadal, elderly men (> 65 years of age) with evidence of decreased physical function, sexual function, or vitality will positively impact these endpoints versus placebo. The study enrolled 788 men with 1 year of follow-up. In addition to the 3 primary endpoints (physical function, sexual function, and vitality), the study will also assess testosterone pharmacokinetics, as well as the influence of testosterone on anemia, computed tomography angiography, bone density, and cognition. As mentioned above, the study results are expected in the early part of 2015.

Sexual dysfunction and lack of energy have been identified as important symptoms commonly reported by men with hypogonadism.<sup>200-203</sup>



Unfortunately, the ability to assess improvement of these 2 symptoms in clinical trials is limited by the lack of existing patient-reported outcomes instruments that have been developed according to the FDA Guidance.<sup>142</sup> One ongoing study (sponsored by Lilly) was designed to compare the effect of testosterone versus placebo on sexual drive and energy, while psychometrically testing the performance characteristics of 2 new instruments developed according to the FDA Guidance: the SAID Scale and the HED.

Several ongoing observational and epidemiologic studies also aim to characterize the risks of testosterone replacement therapy and are expected to be published by August of 2015 (NIH Grant ID# 5R01AG042845 02, University of North Carolina; NIH Grant ID# 5R01AG042921 02, the Kaiser Foundation; and NIH Grant ID# 5R01AG042934 02, Seattle Institute for Biomedical/Clinical).

### **3.7                      Summary: Hypogonadism, Guidelines, and Benefits of Testosterone Replacement Therapy**

Hypogonadism is an endocrine disorder characterized by absent or deficient testosterone levels along with signs and symptoms of androgen deficiency. The absence or deficiency of testosterone is associated with regression of secondary sex characteristics, impaired sexual function, impaired sense of well-being, muscle wasting and decreased strength, and reduced bone mineral density.

Current guidelines for use of TRT outline the appropriate assessment and monitoring for men who are candidates for testosterone therapy. Key components of the Endocrine Society Guidelines include:

Candidates for TRT should exhibit signs and symptoms consistent with the hypogonadal syndrome and have documented evidence of low testosterone levels.

Following confirmation of low testosterone, patients should be evaluated for comorbid disease states and other causative factors.

Men should be evaluated for acute illnesses and medications that potentially cause temporary reductions in testosterone levels; testosterone levels in these cases are expected to rebound following recovery or cessation of the medication in most instances.

Once the decision is made to initiate TRT, a treatment plan with ongoing assessment of patients' signs and symptoms should be implemented and also should include monitoring of testosterone levels, relevant laboratory assessments, and potential adverse events.

Most of the literature describing the benefits of TRT comes from non-registration studies. Of note, registration studies (i.e., pivotal Phase 3 studies for product approval) are designed to assess the products' ability to raise testosterone levels into the normal range. Several registration programs also explore secondary endpoints (e.g., sexual function), the results of which are generally consistent with non-registration studies. A comprehensive review of the literature indicates benefits for a number of target organs.

Although benefits have been observed across numerous studies, there are some limitations to consider:

The relative absence of large (N > 200), placebo-controlled studies with longer durations follow-up (> 1 year) makes it difficult to interpret the long-term clinical impact of TRT.

The inclusion of heterogeneous patient populations; ranging from highly symptomatic, severely hypogonadal men to men without symptoms in domains of interest who also have low-normal and normal testosterone levels.

A variety of study designs and follow-up durations ranging from randomized, placebo-controlled studies (relatively few) to uncontrolled or observational studies (relatively more) with durations that span months (many) to years (few).

Lack of FDA-validated disease specific questionnaires that specifically assess hypogonadal symptoms like sexual desire, fatigue, and mood.

With that in mind:

The totality of the data consistently support TRT benefits on measures of lean mass, fat mass, and bone mineral density and architecture.

Less consistently, data also suggest benefit with sexual function. Additionally, there is some evidence that suggests benefit with mood and fatigue.

In summary, the reviewed data support potential benefits on a number of hypogonadal signs and symptoms with TRT in appropriately selected men.

The benefits of TRT continue to be evaluated through ongoing clinical research. The scientific understanding of benefits, broadly and in special populations, continues to advance. Guidelines for TRT use may be further refined as new data become available. The T Trial, which should be reported in 2015, will further characterize the benefits of testosterone use in older men and may also provide important information about safety. Likewise, the ongoing SAID and HED work aims to help characterize the benefits in a younger cohort of symptomatic men.

## **4.0 Cardiovascular Risk in Hypogonadal Men**

### **4.1 Cardiovascular Risk Introduction**

The CV risk profile in hypogonadal individuals receiving TRT has been extensively reviewed by the TRT Sponsors.

Evidence considered for this review has been drawn from a variety of sources. First, incidence/prevalence data for the burden of CV adverse events in the general male population versus the hypogonadal male population are compared to evaluate whether hypogonadal individuals are at an increased risk of experiencing CV adverse outcomes regardless of TRT administration. Then, data from relevant TRT placebo-controlled studies, meta-analyses, and observational studies are presented and critically appraised.

Full details of the various data sources, the evidence they provide, and the TRT Sponsors' assessment of the findings can be found in the subsections that follow. In summary, the

TRT Sponsors' overall conclusions following a detailed, methodical review of the data are as follows:

Studies suggest a higher prevalence of baseline CV events and CV risk factors among hypogonadal males compared with the general male population.

The prevalence of baseline CV comorbidities is higher among hypogonadal men prior to receiving TRT compared with hypogonadal men who remain untreated.<sup>204</sup> Given these findings, treated hypogonadal individuals are expected to have higher risk of CV events related to the severity of the underlying disease state.

To date, there have been no large randomized, placebo-controlled, CV outcomes clinical trials of TRT. Placebo-controlled studies of testosterone replacement in hypogonadal individuals are summarized, the majority of which do not suggest an association between testosterone use and CV adverse outcomes. The one study that suggests a possible association (**Basaria et al**<sup>115</sup>) is weakened by a number of limitations including the broad, nonspecific definition of CV events (such as edema, syncope, and hypertension), the confounding effects of marked baseline differences between treatment groups favoring the placebo group, and ascertainment bias on account of CV events not being a planned outcome; in fact, the authors themselves comment that, given the small numbers, their findings may be due to chance.

Eight meta-analyses were published investigating the possibility of an association between TRT and CV risk factors or CV events. Only one (**Xu et al 2013**<sup>205</sup>) of these meta-analyses reported an association between CV events and TRT; this result was largely driven by the single **Basaria et al** study described previously, and the meta-analysis is limited by the exclusion of relevant studies, questionable event-collection methodology, discrepancies in the event counts compared with the primary publications, and an inappropriate meta-analysis methodology.

Outcomes from available observational studies have been reviewed. The majority do not support an association between TRT and CV events. Two observational studies do report an association (**Finkle et al**<sup>3</sup> and **Vigen et al**<sup>2</sup>). However, based on descriptive analyses (**Li et al 2014**<sup>206</sup>), findings by **Finkle et al**<sup>3</sup> are likely related to underlying hypogonadism rather than testosterone therapy. Also, the limited magnitude of the **Vigen et al**<sup>2</sup> findings plus measured and unmeasured confounding factors influencing patient treatment status and CV risk do not support causality.

On the basis of a systematic review of the of the available TRT literature, the TRT Sponsors found insufficient evidence to support an association between testosterone use and an increased risk of CV events.

## 4.2 Cardiovascular Background

A number of epidemiological studies have demonstrated an association between endogenously low serum testosterone levels and CV events including all-cause mortality.<sup>207-220</sup> Furthermore, several epidemiologic studies have shown an association of low testosterone levels with higher all-cause mortality, particularly mortality due to CV diseases.<sup>208-210</sup> Some data suggest that testosterone may improve CV health through beneficial changes in fat mass, insulin sensitivity, and lipid profiles; or by its anti-inflammatory and anticoagulant properties.<sup>175,221-222</sup> Other effects such as sodium retention, congestive heart failure, and adverse changes in HDL cholesterol may indirectly or directly be less favorable to CV health.

A complicating factor in the interpretation of published studies in this area is an inconsistency in the way that CV events are defined in the various studies. Some studies used a broad definition of CV disorders consistent with definitions by the American Heart Association (AHA). According to the AHA, CVD includes the following: CV death, coronary artery disease (CAD), MI, angina pectoris [leading to hospitalization (with or without coronary revascularization)], stroke, heart failure (HF), and uncontrolled hypertension (HTN).<sup>223</sup> The nonfatal conditions are used as the basis for the determination of individual underlying risk for experiencing a major adverse cardiac

event (MACE) and for the epidemiological evaluation of incidence and prevalence of CV disease. However, the most recent publications have focused on a more narrow definition of MACE, i.e., MI, stroke, and death (either all-cause mortality or CV mortality), as they are easier to adjudicate by expert endpoint committees.

To date there have been no randomized, placebo-controlled CV outcomes clinical trials evaluating TRT. In 2010, a placebo-controlled study (TOM trial) by **Basaria et al**,<sup>115</sup> in frail men > 65 years of age, was stopped early because of an imbalance in CV associated adverse events in the TRT arm compared with the placebo-treated arm. The CV events were not a planned outcome, and the data safety monitoring board (DSMB) combined a number of event terms such as chest pain, syncope, and abnormal findings on stress tests under an umbrella termed "CV-related events." The CV adverse events were confirmed by the DSMB (see Section 4.6.1 for more details). Previously, similar trials had not shown an increased risk of adverse CV events with testosterone therapy.<sup>114,224</sup>

A number of meta-analyses have suggested that TRT has effects on individual CV risk factor measures (both positive and negative) but do not demonstrate consistent effects on CV events or on MACE.<sup>76,225-229,249</sup> Perhaps due in part to limited size and design, these studies do not demonstrate patterns indicative of patient characteristics (age and comorbidities), formulation, or duration of therapy playing a role in relationships between testosterone and CV events. Meta-analyses that estimate increases in CV events define CV events broadly and include events such as edema and HTN as outcomes. Combining disparate, nonspecific outcomes that are not pathophysiologically related does not provide clinically meaningful information about risk of MACE (MI, stroke, and death, either all-cause mortality or CV mortality). Although not adequately powered or designed for this purpose, the results of other published meta-analyses specifically focused on MACE outcomes do not show consistent effects of adequate magnitude to warrant the findings to be classified as a risk or having any impact on the overall benefits and risks assessment. Seven meta-analyses on pooled randomized controlled trials (RCTs) show no statistically significant associations between TRT and CV events, while Xu et al<sup>205</sup> alone reported that TRT is associated with higher risk of a CV-related event [odds ratio (OR) = 1.54; 95%

CI: 1.09, 2.18]. The one positive study had limitations, including the broad definition of CV outcomes (including outcomes not specific to MACE, such as edema and hematocrit > 50%) and discrepancies between the authors' report of event counts compared with that reported in primary publications (e.g., **Basaria et al 2010**<sup>115</sup> and **Srinivas-Shankar et al 2010**<sup>114</sup>) (see Section 4.6.2 for more details).

The CV safety of TRT in hypogonadal men has been characterized in a number of published observational studies (details in Section 4.6). Although much of the data indicate that TRT does not result in an increased risk of CV events, two recently published retrospective, observational studies (**Vigen et al 2013**<sup>2</sup> and **Finkle et al 2014**<sup>3</sup>) each suggested an increased risk of CV events among groups of men prescribed testosterone therapy. However, both studies had important and substantial limitations that bring into question the validity of the results and weaken their value for confirming a causal relationship between TRT and adverse CV events (see Section 4.6.3 for a detailed review).

This review is aimed to provide a systematic literature review and comprehensive evaluation of any association between TRT use and CV risk.

### **4.3 Incidence and Prevalence of Cardiovascular Events**

Incidence and prevalence numbers for the general category "CVD" are difficult to obtain since most data relate to the specific subtypes of CVD.

A report from the AHA indicated that in US, men aged 20 years and older in 2006:

The prevalence of CVD was 37.9% (non-Hispanic [NH] whites, 38.1%; NH blacks, 44.6%; Mexican Americans, 28.5%). The average annual rates of first CV events increased from 3 per 1,000 men aged 35 to 44 years to 74 per 1,000 men 85 to 94 years of age.

The overall any-mention death rates for CVD were 306.6 for white males and 422.8 for black males per 100,000, respectively.<sup>223</sup>

An estimated 4.7% of US men had an MI (NH whites, 5.1%; NH blacks, 3.6%; Mexican Americans, 2.6%).<sup>223</sup>

The prevalence of HF was 3.1% (NH whites, 3.2%; NH blacks, 3.0%; Mexican Americans, 1.7%).

The annual rates per 1,000 population of new HF events were as shown in Table 12.

**Table 12. Annual Rates of Heart Failure per 1,000 Population in 2006**

Age Group, years	White Men	Black Men
65 – 74	15.2	16.9
75 – 84	31.7	25.5
85	65.2	50.6

The overall any-mention death rates for HF were 103.7 for white males and 105.9 for black males per 100,000, respectively.<sup>223</sup>

The prevalence of CHD was 9.1% (NH whites, 9.4%; NH blacks, 7.8%; Mexican Americans, 5.3%). On the basis of 1987 to 2001 data from the Atherosclerosis and Risk in Communities (ARIC) study of the National Heart, Lung, and Blood Institute (NHLBI), the annual rates of new episodes of CHD per 1,000 men 45 to 64 years of age were 12.5 for nonblack men and 10.6 for black men. Hypertension and diabetes mellitus were risk factors for CHD (hazard ratio [HR] = 2.0 for HTN in black men and 1.6 in white men; HR = 1.6 for diabetes in black men and 2.0 in white men). The age-adjusted death rates (per 100,000) for CHD were 176.3 for white males, 206.4 for black males, 132.8 for Hispanic or Latino males, 122.4 for American Indian or Alaska Native males, and 101.3 for Asian or Pacific Islander males. Other risk factors for CHD include high cholesterol, smoking, low physical activity, and increased BMI.<sup>223</sup>

The estimated prevalence of stroke was 2.5% (NH whites, 2.3%; NH blacks, 3.8%; Mexican Americans, 2.8%). Of all strokes, 87% were ischemic and 13% were hemorrhagic. Death rates for stroke per 100,000 were 41.7 for white males and 67.1 for black males.<sup>223</sup>



The annual rates per 1,000 population of new episodes of angina pectoris for nonblack men were 28.3 for those 65 to 74 years of age, 36.3 for those 75 to 84 years of age, and 33.0 for those 85 years and older. For black men, the rates were 22.4, 33.8, and 39.5, respectively. On the basis of 1987 to 2001 data from the ARIC study of the NHLBI, the annual rates per 1,000 men of new episodes of angina pectoris for nonblack men were 8.5 for those 45 to 54 years of age, 11.9 for those 55 to 64 years of age, and 13.7 for those 65 to 74 years of age. For black men, the rates were 11.8, 10.6, and 8.8, respectively.<sup>223</sup> The prevalence of angina pectoris in US adult males aged 20 years and older was 4.6% (NH whites, 4.7%; NH blacks, 4.0%).<sup>223</sup>

The prevalence, incidence, and death rates of CV events in the US general population, according to the AHA, are listed in [Appendix A](#).<sup>223</sup>

#### **4.3.1 Cardiovascular Events in the Hypogonadal Male Population**

The prevalence, incidence, and death rates of CV events in the hypogonadal male population are listed in [Table 13](#).

**Table 13. Cardiovascular Events in the Hypogonadal Male Population**

CV Events in Hypogonadal Males	Prevalence at Baseline, %	Incidence per 1,000 Person Years	Deaths per 100,000 Population
CVD <sup>a</sup>			520 <sup>208,231</sup> (worldwide)
Frail men 65 years of age and older (mean age 74)	50 (53 T group; 47 placebo) <sup>115</sup> (US)		
CHD			
Age 40 yrs	21 (20.1 T group; 23.1 untreated) <sup>232</sup> (US)		
Hypertension			
Frail men 65 years of age and older (mean age 74)	85 T group; 78 placebo <sup>115</sup>		
Age 52.3 – 73.2 yrs (mean 63.1 yrs)	43.3 <sup>208</sup> untreated (Germany)		
Hyperlipidemia			
Frail men 65 years of age and older (mean age 74)	56 (63 T group; 50 placebo) <sup>115</sup> (US)		
Age 45 yrs	85.9 untreated; 88.3 treated <sup>2</sup>		
Coronary artery disease			
40 yrs	21.7 <sup>287</sup> (Low T overall; treatment data not available) (US)		
MI			
Age 52.3 – 79.2 yrs (mean 63.1 yrs)	6.3 <sup>208</sup> untreated (Germany)		
Age 45 yrs	20 <sup>2</sup> (TRT 24.3; no TRT 20.3) (US)	7.4 (TRT) – 8.3 (placebo) <sup>288</sup> (worldwide)	

See notes at end of table.

**Table 13. Cardiovascular Events in the Hypogonadal Male Population (Continued)**

CV Events in Hypogonadal Males	Prevalence at Baseline, %	Incidence per 1,000 Person Years	Deaths per 100,000 Population
Stroke/CVA			
Age 52.3 – 79.2 yrs (mean 63.1 yrs)	2.1 untreated <sup>208</sup> (Germany)		
Age 45 yrs		5.5 (TRT) – 11.1 (placebo) <sup>288</sup> (worldwide)	
All CV events			
Age 45 yrs		33.2 (TRT) – 44.3 (placebo) <sup>288</sup> (worldwide)	

CHD = coronary heart disease; CV = cardiovascular; CVA = cerebral vascular accident; CVD = cardiovascular disease; MI = myocardial infarction; T = testosterone; TRT = testosterone replacement therapy; US = United States

- a. CVD includes hypertension, stroke, heart failure, angina pectoris, and coronary artery disease/myocardial infarction.

Further, epidemiological studies suggest that the patient characteristics in terms of CV events and risk factors are different between untreated hypogonadal patients and patients treated with TRT prior to starting treatment. Using claims data from the US, **Li et al**<sup>204</sup> found a higher prevalence of CV events and CV risk factors among males prior to initiating treatment with testosterone compared with those who did not receive testosterone treatment. This observation was replicated using electronic medical records data from the United Kingdom (UK).<sup>204</sup> Therefore, any studies comparing CV outcomes between TRT treated patients and untreated patients should consider the important differences prior to treatment initiation.

In summary, the prevalence of CV events among hypogonadal males is observed to be higher than that of males in general. Moreover, the prevalence of baseline CV comorbidities is higher among hypogonadal men prior to receiving TRT compared with hypogonadal men who remain untreated.<sup>204</sup> Therefore, hypogonadism itself is associated with CV risk, and as such patients selected to receive treatment are at an even greater CV risk prior to initiating TRT.

#### **4.4 Risk Factors for Cardiovascular Events**

Cardiovascular events, or medical conditions resulting from underlying CVD, reflect broad, nonspecific, and sometimes conflicting pathophysiology. Definitive CV outcomes studies focus on MACEs (MI, stroke, and CV death with or without unstable angina and HF) to ensure common pathophysiology, increased specificity, and clinical relevance of endpoint.<sup>233</sup>

Risk factors for CVD include metabolic syndrome, obesity, diabetes, HTN, high cholesterol, smoking, low physical activity, increased BMI, increased age, and high alcohol intake.<sup>223,80</sup> Most patients with CHD have some identifiable risk factor. Such risk factors include a positive family history, male gender, blood lipid abnormalities, diabetes mellitus, HTN, physical inactivity, abdominal obesity, and cigarette smoking.<sup>234</sup>

#### **4.5 Associations Between Hypogonadism and Cardiovascular Events**

Androgen deficiency can modulate vascular function in men; low testosterone levels have been associated with metabolic syndrome, obesity, diabetes, HTN, atherosclerosis, increased fat mass, adverse lipid profile, thrombosis, and insulin resistance.<sup>80</sup>

Longitudinal studies in men without prostate cancer also show that testosterone insufficiency is independently associated with CV mortality.<sup>208-210,218,219,235,236</sup>

##### **4.5.1 Type 2 Diabetes Mellitus, Obesity and Metabolic Syndrome, Hypertension, and Hyperlipidemia**

Type 2 diabetes mellitus (T2DM), obesity, and metabolic syndrome are associated with hypogonadism.<sup>33,231</sup>

Loss of androgen action leads to diabetes, and loss of glycemic control leads to hypogonadism.<sup>237</sup> A complex, bi-directional, interrelationship exists between the conditions.<sup>171</sup> Diabetic subjects have lower testosterone levels (approximately 86 ng/dL) than their counterparts without T2DM.<sup>171</sup> Most middle-aged and older men with symptoms consistent with hypogonadism and low testosterone levels will have one or

more chronic diseases, and many of these men are obese. The Hypogonadism In Males (HIM) study found low free testosterone levels in 25% of the obese subjects and 35% of the diabetic subjects with a strong inverse relationship between testosterone and BMI.<sup>171,238</sup>

In a Finnish study of 702 middle-aged men with 11 years of follow-up, low total testosterone levels independently predicted the development of metabolic syndrome and diabetes.<sup>72</sup> Men with total testosterone levels in the lower fourth were 2.3 times more likely to develop metabolic syndrome or diabetes than other men after adjustment for age (OR for metabolic syndrome = 2.3; 95% CI: 1.5, 3.4; OR for diabetes = 2.3; 95% CI: 1.3, 4.1).<sup>72</sup> **Mulligan et al**<sup>33</sup> examined the prevalence rates and the risk of selected comorbidities associated with hypogonadism in 2,162 primary care patients. The ORs for the presence of hypogonadism were 2.38 for obesity, 2.09 for diabetes, 1.84 for HTN, and 1.47 for hyperlipidemia. The relative association of hypogonadism increased the most with increasing BMI (OR = 1.65 per 5-unit BMI increase). The prevalence of hypogonadism was 52.4% and 50.0% in men who were obese and diabetic, respectively.<sup>33</sup>

#### **4.5.2 Coronary Artery Disease**

Associations between the prevalence of CAD and testosterone levels are mixed. Results of these studies are summarized in [Table 14](#).

**Table 14. Summary of Studies Reporting on Low Testosterone and Coronary Artery Disease**

Author/Study	T Measurement	CV Event (Method)	Main Finding of Study
Studies showing an association between low testosterone level and incident CAD <sup>289</sup>			
Zhao et al <sup>212</sup> (CCS, n = 201)	TT	CAD (H&P, ECG, cardiac catheterization in 27 patients)	Men with CAD have lower levels of TT
English et al <sup>213</sup> (CCS, n = 90)	TT, FT, BT, FAI	CAD (cardiac catheterization)	Men with catheterization-proven CAD have lower levels of FT, BT, and FAI
Dobrzycki et al <sup>214</sup> (CCS, n = 96)	TT, FT, FAI	CAD (cardiac catheterization)	Men with catheterization-proven CAD have lower levels of TT, FT, and FAI
Akishita et al <sup>215</sup> (CS, n = 171)	TT	CV events <sup>a</sup> (H&P, physician and hospital records)	Men with lower levels of endogenous TT are more likely to suffer CV events
Rosano et al <sup>216</sup> (CCS, n = 129)	TT, FT, BT	CAD (cardiac catheterization)	Men with catheterization-proven CAD have lower levels of TT and BT
Hu et al <sup>217</sup> (CCS, n = 87)	TT	CAD (cardiac catheterization)	Men with catheterization-proven CAD have lower levels of TT

See notes at end of table.

**Table 14. Summary of Studies Reporting on Testosterone and Coronary Artery Disease (Continued)**

Author/Study	T Measurement	CV Event (Method)	Main Finding of Study
Studies not showing an association between low testosterone level and incident CAD <sup>289</sup>			
Cauley et al <sup>239</sup> (CCS, n = 163)	TT, FT	Acute, nonfatal MI, death from CV disease (ECG, hospital records)	No difference in TT or FT levels between cases and controls
Barrett-Connor et al <sup>240</sup> (CS, n = 1009)	TT	CV disease or mortality, ischemic heart disease morbidity or mortality (death certificates, hospital records)	No statistically significant association between levels of TT and primary end points
Kabakci et al <sup>241</sup> (CCS, n = 337)	TT, FT	CAD (cardiac catheterization)	No statistically significant difference in FT or TT levels between cases and controls
Arnlov et al <sup>242</sup> (PCS, n = 2084)	TT	CV disease <sup>b</sup> (physician and hospital records)	No significant association between levels of endogenous TT and incidence of CAD

BT = bioavailable testosterone; CAD = coronary artery disease; CCS = case-control study; CS = cohort study; CV = cardiovascular; ECG = electrocardiogram; FAI = free androgen index; FT = free testosterone; H&P = history and physical; MI = myocardial infarction; PCS = placebo-controlled study; TT = total testosterone

- Cardiovascular events include stroke, coronary artery disease, sudden cardiac death, and peripheral arterial disease.
- Cardiovascular disease includes coronary artery disease, myocardial infarction, angina pectoris, coronary insufficiency, death from coronary artery disease, stroke, transient ischemic attack, congestive heart failure, and peripheral vascular disease.

### 4.5.3 Cardiovascular and All-Cause Mortality

Multiple studies have reported an increased risk of CV death in men with low serum testosterone levels. These studies are detailed in [Table 15](#).

**Table 15. Association of Testosterone Levels with Cardiovascular and All-Cause Mortality<sup>a</sup>**

Study	Nature of Study	Men in Study	Age Range (mean)	Follow-Up (yrs)	HR CV Mortality (95% CI)	HR All-Cause Mortality (95% CI)	Summary
Haring et al 2010 <sup>208</sup>	Prospective	1,954	20 – 79 (58.7)	7.2	TT: 2.56 (1.15, 6.52)	TT: 2.32 (1.38, 3.89)	Low TT is associated with higher risk of all-cause and CV mortality
Khaw et al 2007 <sup>209</sup>	Prospective	2,314 of 11,606	40 – 79 (67.3)	10	TT: 2.29 (1.60, 3.26)		Low TT is associated with higher risk of all-cause and CV mortality
Laughlin et al 2008 <sup>210</sup>	Prospective	794	63 – 78.9 (71.2)	20	TT: 1.38 (1.02, 1.85) BT: 1.36 (1.04, 1.79)	TT: 1.44 BT: 1.50	Low TT and BT are associated with higher risk of all-cause and CV mortality
Malkin 2010 <sup>218</sup>	Prospective	930	Not reported	6.9	BT: 2.2 (1.2, 3.9)	BT: 2.27 (1.45, 3.60)	Low BT is inversely associated with time to all-cause and CV mortality
Menke et al 2010 <sup>219</sup>	Prospective	1,114	20 (40)	9	FT: 1.53 (1.05, 2.23) BT: 1.63 (1.12, 2.37)	FT: 1.43 (1.09, 1.87) BT: 1.52 (1.15, 2.02)	Decrease in FT and BT from 90 <sup>th</sup> to 10 <sup>th</sup> percentile are associated with increased risk of all-cause and CV mortality during the first 9 years of follow-up
Tivesten et al 2009 <sup>220</sup>	Prospective	3,014	69 – 80 (75.4)	4.5	1.65 (1.29, 2.12)		Increasing levels of TT and FT are associated with decreasing risk of all-cause mortality
Corona et al 2010 <sup>235</sup>	Prospective	1,687		4.3	7.1 (1.8, 28.6)		Low T is associated with higher risk of CV mortality

See notes at end of table.



**Table 15. Association of Testosterone Levels with Cardiovascular and All-Cause Mortality<sup>a</sup> (Continued)**

Study	Nature of Study	Men in Study	Age Range (mean)	Follow-Up (yrs)	HR CV Mortality (95% CI)	HR All-Cause Mortality (95% CI)	Summary
Hyde et al 2012 <sup>236</sup>	Prospective	3,637	70 – 88 (77)	5.1	1.62 (1.20, 2.19)		Low T is associated with higher risk of CV mortality
Vikan 2009 <sup>243</sup>	Prospective	1,568	Not reported	11.2		FT: 1.24 (1.01, 1.54)	Low FT is associated with higher risk of all-cause mortality
Shores et al 2006 <sup>244</sup>	Retrospective	858	(59.6)	8		TT: 1.88 (1.34, 2.63)	Low TT is associated with higher risk of all-cause mortality
Pye et al 2014 <sup>245</sup>	Prospective	2,599	40 (61.4)	4.3		2.3 (1.2, 4.2)	Low T is associated with higher risk of all-cause mortality
Muraleedharan et al 2013 <sup>246</sup>	Prospective	581	40 – 79 (60)	5.8		2.3 (1.3, 3.9)	Low T is associated with higher risk of all-cause mortality
Yeap et al 2014 <sup>207</sup>	Prospective	1920 of 2143	70 -89	mean = 6.7 median = 7.1		T: quartile [Q] Q2:Q1 = 0.82 (0.69, 0.98); Q3:Q1 = 0.78 (0.65, 0.94); Q4:Q1 = 0.86 (0.72, 1.04)	U-shaped association between TT and all-cause mortality

BT = bioavailable testosterone; CI = confidence interval; CV = cardiovascular; FT = free testosterone; HR = hazard ratio; T = testosterone; TT = total testosterone; yrs = years

a Traish et al (2014)<sup>211</sup>

## 4.6 Evaluation of Testosterone Replacement Therapy and Cardiovascular-Related Events

Two retrospective, observational studies (**Vigen et al**<sup>2</sup> and **Finkle et al**<sup>3</sup>) have raised questions related to TRT CV safety in patients older than 65 years or with underlying heart disease. However, careful analyses of these studies show that the design of each limits the conclusions that can be drawn about the relationship between CVD and TRT in these populations. Furthermore, other studies do not suggest a higher risk of CV events in these same populations. Men with hypogonadism, or those > 65 years of age, or with prior CV events are at an increased baseline risk of CV events, but currently available evidence does not suggest that TRT increases this risk ([Appendix A](#)). Relevant studies discussed are summarized in [Appendix B](#).

Several TRT trials included in meta-analyses were conducted in men with heart failure, CAD, obstructive sleep apnea, COPD, alcoholic cirrhosis, chronic renal disease on dialysis, and rheumatoid arthritis; all are conditions for which the prescribing information provides warnings and precautions and/or suggestions that the condition(s) be discussed with the consumer's health care provider. Inclusion of patients with these conditions limits interpretation and generalization of results.<sup>229</sup>

### 4.6.1 Placebo-Controlled Studies

A randomized, placebo-controlled 6-month trial (TOM trial) among frail men 65 years of age and older was terminated early because of increased CV-related events in the testosterone-treated group.<sup>115</sup> Participants in the study were required to have evidence of limitations in mobility, defined as having difficulty walking 2 blocks on a level surface or climbing 10 steps and having a score between 4 and 9 on the Short Physical Performance Battery (which measures performance on a scale of 0 to 12, with higher scores indicating better performance). Twenty-three of the 106 subjects in the testosterone group, compared with 5 of the 103 subjects in the placebo group, had cardiovascular-related adverse events. Four MACE events (3 MIs, including 1 death from suspected MI, and 1 stroke) occurred in the testosterone group, with no such events in the placebo group. Thus, the authors conclude that testosterone therapy may increase the risk of cardiac

events in elderly, frail men. However, there are important limitations of this study including post hoc nonspecific CV event definitions (e.g., HTN, syncope, and edema) and ascertainment and aggressive dosing regimen. Most importantly, the authors conclude, "The small size of the trial and the unique population prevent broader inferences from being made about the safety of testosterone therapy." The 2 groups of men also had different baseline characteristics, with a higher rate of hyperlipidemia, and greater use of antihypertensive agents and statins in participants randomized to the testosterone group. Further, CV events were not a planned outcome in this study and were not uniformly queried or collected, a fact that may have introduced an ascertainment bias. Early termination of the trial may overestimate treatment differences.<sup>99,115</sup>

Previous similar trials and meta-analyses have not shown an increased risk of adverse CV events with testosterone therapy.<sup>114,225</sup> A trial by Srinivas-Shankar et al, which was very similar in design, methods, and subjects ("Intermediate-frail to frail, elderly hypogonadal male"; albeit less frail) to the TOM trial showed a low incidence of adverse cardiac events that was not different between the testosterone- and placebo-treated groups.<sup>99, 114</sup>

A randomized, placebo-controlled study in 167 men with a mean age of 66 years showed fewer CV serious adverse events in the testosterone-treated (n = 3 of 96 subjects, 3%) versus the placebo group (n = 10 of 47 subjects, 21%;  $P < 0.001$ ), despite more non-CV serious adverse events (SAEs) in the testosterone group (n = 68 of 96 subjects, 71%) versus the placebo group (n = 20 of 47 subjects, 43%;  $P < 0.003$ ); however, the sample size of this trial should be considered in interpreting these results.<sup>99</sup> A randomized placebo controlled study by Kenny et al<sup>224</sup> on the effects of testosterone on bone density and muscle strength in 131 men (mean age 77.1) (69 received testosterone gel and 62 received placebo) for 12 months. After 1 year of follow-up, there were 3 deaths in the testosterone treated group compared with 7 deaths in the placebo group. Although the cause of death was not specified for each group, the 10 deaths were attributed as follows: sudden death (4), stroke (3), complications following hip fracture or fall (2), and cancer (1). The authors reported that other CV events did not differ between testosterone and placebo.

#### **4.6.2                    Meta-Analyses of Testosterone Replacement Therapy and Cardiovascular Events or Cardiovascular Risk Factors**

Eight meta-analyses evaluating the safety of TRT and CV related events (5) or CV risk factors (3) have been published. These are briefly described in [Table 16](#) below.

**Table 16. Published Meta-Analyses of Studies Examining Testosterone Replacement Therapy and Broadly Defined Cardiovascular-Related Events**

Endpoint	Measure (TRT vs Placebo / Control)	Estimated Magnitude of Measure (95% CI) <sup>a</sup>	Source	N <sup>b</sup>
<b>Event</b>				
Myocardial Infarction (MI)	Relative Risk	0.91 (0.29, 2.82)	Fernández-Balsells et al 2010 <sup>225</sup>	1053
	Odds Ratio	0.99 (0.44, 2.26)	Calof et al 2005 <sup>226</sup>	1070
	Odds Ratio	2.24 (0.50, 10.02)	Haddad et al 2007 <sup>228</sup>	308
Vascular Events / Cerebrovascular Accidents	Odds Ratio	0.86 (0.38, 1.95)	Calof et al 2005 <sup>226</sup>	1070
Coronary Artery Bypass Graft (CABG)	Relative Risk	1.35 (0.26, 6.96)	Fernández-Balsells et al 2010 <sup>225</sup>	158
CABG or other Coronary Procedure	Odds Ratio	0.79 (0.35, 1.79)	Calof et al 2005 <sup>226</sup>	1070
Chest Pain or Ischemia	Odds Ratio	0.93 (0.39, 2.26)	Calof et al 2005 <sup>226</sup>	1070
Arrhythmia	Relative Risk	3.00 (0.32, 27.94)	Fernández-Balsells et al 2010 <sup>225</sup>	54
Atrial Fibrillation or Arrhythmia	Odds Ratio	1.22 (0.53, 2.81)	Calof et al 2005 <sup>226</sup>	1070
<b>Death</b>				
All-Cause Death	Relative Risk	1.12 (0.70, 1.81)	Fernández-Balsells et al 2010 <sup>225</sup>	476
Cardiovascular-related Death	Odds Ratio	1.42 (0.70, 2.89)	Xu et al 2013 <sup>205</sup>	2994

See notes at end of table.

**Table 16. Published Meta-Analyses of Studies Examining Testosterone Replacement Therapy and Broadly Defined Cardiovascular-Related Events (Continued)**

Endpoint	Measure (TRT vs Placebo / Control)	Estimated Magnitude of Measure (95% CI) <sup>a</sup>	Source	N <sup>b</sup>
<b>Combined Cardiovascular Events</b>				
Combined Cardiovascular Events <sup>c</sup> – ALL	Odds Ratio	1.14 (0.59, 2.20)	Calof et al 2005 <sup>226</sup>	1070
Combined Cardiovascular Events <sup>d</sup> – ALL	Relative Risk	1.64 (0.77, 3.47)	Ruige et al 2013 <sup>229</sup>	2137
<b><i>Combined Cardiovascular Events<sup>e</sup> – ALL</i></b>	<b><i>Odds Ratio</i></b>	<b><i>1.54 (1.09, 2.18)</i></b>	<b><i>Xu et al 2013<sup>205</sup></i></b>	<b><i>2994</i></b>
Combined Cardiovascular Events <sup>f</sup> – ALL	Odds Ratio	1.82 (0.78, 4.23)	Haddad et al 2007 <sup>228</sup>	308
<b><i>Combined Cardiovascular Events<sup>g</sup> – SERIOUS</i></b>	<b><i>Odds Ratio</i></b>	<b><i>1.61 (1.01, 2.56)</i></b>	<b><i>Xu et al 2013<sup>205</sup></i></b>	<b><i>2994</i></b>

CABG = coronary artery bypass graft; CI = confidence interval; CV = cardiovascular; MI = myocardial infarction; N = number of pooled patients; TRT = testosterone replacement therapy. Bold font = statistically significant.

- Values presented in italic boldface type achieved statistical significance.
- With the exception of the information obtained from Ruige et al 2013, all of these values represent the number of pooled patients in the cited study.
- Includes the following events: hematocrit >50%; atrial fibrillation/arrhythmia; MI; chest pain/ischaemia; coronary procedure/CABG; vascular/cerebrovascular events.
- The events included (in order of frequency of occurrence): arrhythmia, hypertension, MI, peripheral oedema, coronary artery bypass graft, thrombosis, cardiovascular complaints, heart failure, chest pain, vascular events, syncope, stroke, pulmonary embolism and abdominal aneurysm.
- CV events included: anything reported as such by the authors, that is, events reported as cardiac disorders, cardiovascular complaints, cardiovascular events, vascular disorders, cardiac or cardiovascular, or where the event description fell within the International Statistical Classification of Disease version 10 chapter IX (100 to 199).
- Includes: cardiovascular death, fatal and nonfatal myocardial infarction and other CV events (e.g., angina, arrhythmia, revascularization procedures, stroke).
- Cardiovascular-related events which the authors described as serious adverse events or where the outcome was death, life-threatening, hospitalization, involved permanent damage or required medical/surgical intervention, or was one of the following types of cardiovascular event: myocardial infarction, unstable angina, coronary revascularization, coronary artery disease, arrhythmias, transient ischemic attacks, stroke or congestive heart failure but not deep vein thrombosis.

#### 4.6.2.1            **Meta-Analyses of Testosterone Replacement Therapy and Cardiovascular Events**

A meta-analysis of 19 randomized clinical trials was conducted by **Calof et al**<sup>226</sup> to determine the risks of adverse events associated with TRT in men > 45 years of age with low or low-normal testosterone levels. Comparing the testosterone replacement group to placebo, the OR for all cardiac events was not significant (OR = 1.14; 95% CI: 0.59, 2.20), with an incidence of 33.2 and 44.3 per 1,000 PY in the testosterone-treated and placebo groups, respectively. No significant differences were found in the rates of atrial fibrillation/arrhythmia, MI, chest pain/ischemia, coronary procedures or vascular events/cerebrovascular accidents between the testosterone and the placebo/nonintervention groups.<sup>226</sup>

**Haddad et al**<sup>228</sup> conducted a systematic review and meta-analysis of randomized trials that assessed the effect of testosterone use on CV events (CV death, fatal and nonfatal MI, and other CV events including angina, arrhythmia, revascularization procedures, stroke) in men with different degrees of androgen deficiency. Thirty trials were included, with 6 trials reporting on CV events. No significant differences were found among men receiving TRT compared with the control groups (OR any CV event = 1.82; 95% CI: 0.78, 4.23; OR fatal and nonfatal MI = 2.24; 95% CI: 0.50, 10.02). Testosterone use in men with low testosterone levels led to changes in blood pressure and in all lipid fractions (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides). Results were similar in patients with low-normal to normal testosterone levels.

**Fernández-Balsells et al**<sup>225</sup> found no significant differences in the rates of death, MI, revascularization procedures, or cardiac arrhythmias between the testosterone and the placebo/nonintervention groups in a meta-analysis of 51 randomized and nonrandomized placebo-controlled trials. The testosterone and placebo/nonintervention groups did not differ significantly in the incidence of diabetes mellitus or in the changes from baseline in cardio-metabolic risk factors, such as fasting glucose, total and LDL cholesterol, triglycerides, and systolic and diastolic blood pressure levels. There was a statistically significant reduction in HDL cholesterol in the men receiving testosterone therapy.<sup>225</sup>

**Ruige et al 2013**<sup>229</sup> conducted a meta-analysis of 10 RCTs that each included more than 100 participants to evaluate the effect of testosterone treatment on CV risk. Overall, no statistically significant difference between placebo and testosterone treatment was found for testosterone treatment and CV-risk (relative risk = 1.64; 95% CI: 0.77, 3.47).

**Xu et al**<sup>205</sup> conducted a systematic review and meta-analysis of placebo-controlled randomized trials of testosterone therapy published through 2012 among men lasting 12+ weeks reporting CV-related events. The 27 trials included 2,994 mostly middle-aged or older men (1,733 testosterone and 1,261 placebo) with low testosterone and/or chronic diseases, who experienced 180 CV-related events; 33 CV-related deaths were identified (22 testosterone arm and 11 placebo arm), for which the OR was similar (OR = 1.42; 95% CI: 0.70, 2.89) to the estimate for all CV-related events. The authors reported an increased risk of CV-related events in the testosterone population (OR = 1.54; 95% CI: 1.09, 2.18); however, only one<sup>115</sup> of the 27 studies found a statistically significant increase. The TOM trial<sup>115</sup> that reported an increased risk has been discussed previously with details on the limitations. An internal re-analysis revealed that if the TOM trial were excluded from the meta-analysis, using the same method as indicated in Xu et al, the OR would decrease from 1.54 to 1.28 (95% CI: 0.88, 1.85).

The Xu et al meta-analysis had a large range of differences among the included studies: age (18 to > 80 years); treatment time (12 weeks to 3 years); initial testosterone levels (7.3 to 21.1 nmol/L); number of subjects (11 to 316); dose and method of administration (injection, gel, patch, oral) and comorbidities/health status (alcoholic cirrhosis, chronic renal disease on dialysis, rheumatoid arthritis, cognitive decline, malnutrition, frailty, coronary artery disease, heart failure, metabolic syndrome or T2DM, obesity, obstructive sleep apnea, erectile dysfunction, and COPD). In particular, the Copenhagen study, which was the second most heavily weighted study included in this meta-analysis, was conducted on alcoholic cirrhotic patients and included esophageal varices as CV events, and thus, it should have been excluded from a meta-analysis intended to evaluate CV events. Further, it is unlikely that either the Copenhagen cohort or the TOM cohort (frail)



are representative of a substantial portion of current testosterone replacement therapy users (Section 5.5 and Section 5.7).

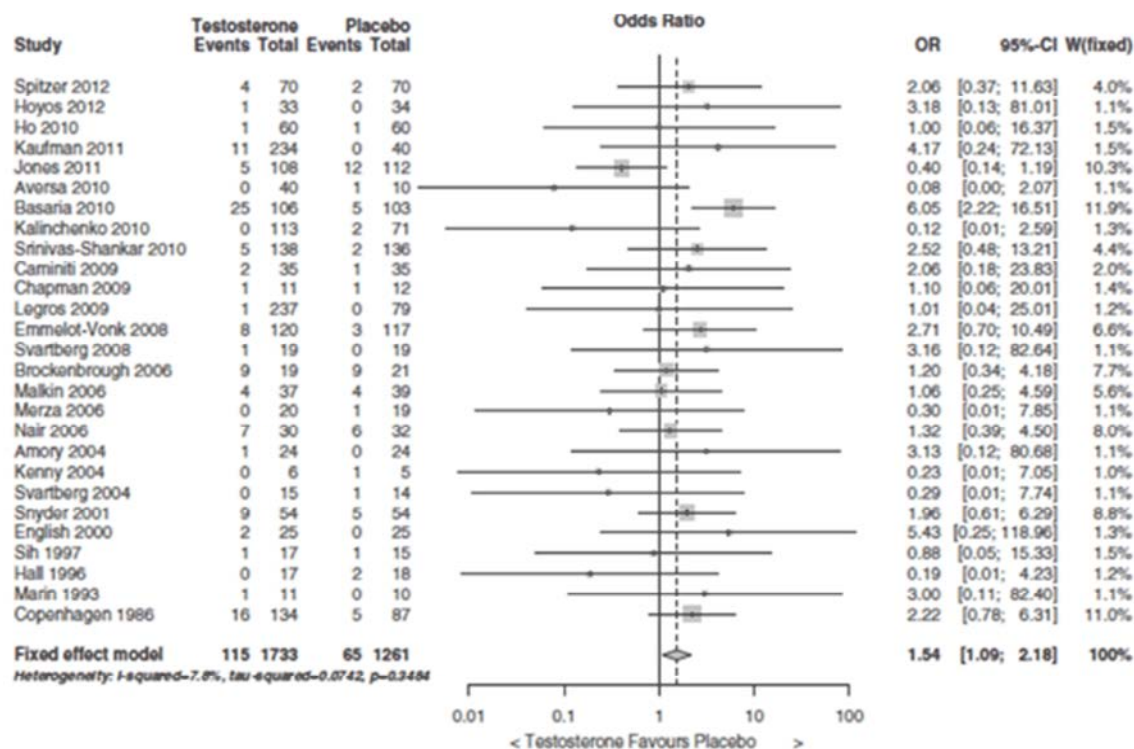
Xu et al utilized a fixed-effect model approach in the analysis of the data from 27 studies. Although lack of fit tests for testing heterogeneity across 27 studies were performed, it is well known that such tests lack of power to detect the model misspecification to justify the validity of the fixed-effect modeling approach. For the studies considered in Xu et al, it appears that the empirical OR from the TOM trial is quite different from those from other trials. Therefore, the results Xu et al presented based on a fixed-effect model are questionable. The strength of meta-analyses is that they combine endpoints from smaller studies to offer perspective on outcomes. However, a basic requirement for appropriate meta-analyses is a certain amount of homogeneity between pooled studies (e.g., patient populations, endpoints evaluated, interventions). Thus, meta-analytic procedures will have inherent limitations and require various sensitivity analyses for the totality of evidence on the safety concerns. With the data from the 27 studies, the resulting confidence interval estimates based on the exact inference procedures for the fixed-effect model<sup>248</sup> cannot confirm the findings from Xu et al. Moreover, with a robust random effect model approach,<sup>230</sup> the estimated relative risk (RR) was 1.28 with 95% CI: 0.88, 1.85, indicating that the results are consistent with previous meta-analyses.

In addition, CV-related events were defined as anything reported as such by the authors, i.e., events reported as cardiac disorders, CV complaints, CV events, vascular disorders, cardiac or CV, or where the event description fell within the ICD-10 codes (I00 to I99). Serious CV events were defined as CV-related events which the authors described as SAEs or where the outcome was death, life-threatening, hospitalization, involved permanent damage, or required medical/surgical intervention, or was one of the following types of CV event: MI, unstable angina, coronary revascularization, CAD, arrhythmias, transient ischemic attacks, stroke, or congestive heart failure, but not deep vein thrombosis.<sup>205</sup> This study is limited by the broad definition of CV outcomes (including outcomes not specific to MACE, such as syncope and edema), exclusion of relevant studies, and concerns about the methodology. The methods used were appropriate for

combining outcomes of patients with events, but the authors appear to have extracted patients with events from some studies and event counts from other studies. Also, there were discrepancies between the authors' report of event counts compared with that reported in primary publications (e.g., Basaria et al 2010<sup>115</sup> and Srinivas-Shankar et al 2010<sup>114</sup>).

A forest plot of the 27 clinical trials included in Xu et al<sup>205</sup> meta-analysis is presented in Figure 5. This plot depicts visually that the studies show a pattern of markedly variable point estimates in both directions rather than a consistent trend of either higher or lower risk.

**Figure 5. Forest Plots of Placebo-Controlled Randomized Trials Examining the Pooled Effect of Testosterone Replacement Therapy on Cardiovascular-Related Events**



Source: Xu et al 2013<sup>205</sup>

#### 4.6.2.2                    **Meta-Analyses of Testosterone Replacement Therapy and Cardiovascular Risk Factors**

**Isidori et al 2005**<sup>76</sup> conducted a meta-analysis of RCTs and evaluated several endpoints associated with testosterone treatment including serum lipid profile in men < 49 years. In 16 RCTs with reported total cholesterol, testosterone treatment reduced total cholesterol by 0.23 mmol/L (95% CI: -0.37, -0.10) overall with a greater effect size reported in studies with hypogonadal men than in studies with eugonadal men; there was no change in LDL cholesterol in the 11 RCTs that reported LDL cholesterol. A potential reduction in HDL cholesterol was reported in the group of 8 studies with men having a higher baseline testosterone, but the overall effect on HDL cholesterol and testosterone treatment was not statistically significant among all 13 studies that included data on HDL cholesterol.

**Corona et al 2011**<sup>227</sup> evaluated the association between testosterone and CV risk using cross-sectional studies (54) and prospective studies (10) in addition to a specific meta-analysis on the potential benefit of testosterone treatment on CV endpoints using 6 RCTs. In the cross-sectional study analysis, after adjusting for age, BMI, diabetes, and HTN, the presence of any CVD was associated with lower total testosterone levels (HR = 0.536; 95% CI: 0.447, 0.606) and thus, the risk of CV events decreases on average by 1.86 for each nmol/L unit of testosterone increase. Using the 10 prospective studies, baseline total testosterone level was significantly lower among patients with overall and CV-related mortality compared with controls. However, no association was found between testosterone and CV incidence. Among the RCTs, testosterone treatment was positively associated with significant increase in treadmill test duration and time to 1-mm ST segment depression.

**Corona et al 2013**<sup>249</sup> conducted meta-analyses among hypogonadal men with metabolic syndrome (6 RCTs) and T2DM (5 RCTs); they found that testosterone treatment was associated with a statistically significant reduction in triglyceride levels for both men with metabolic syndrome (weighted mean difference in triglycerides was -0.40, 95%

CI: -0.66, -0.14) as well as men with T2DM (weight mean difference in triglycerides was -0.60, 95% CI: -0.83, -0.37).

#### **4.6.3 Observational Studies**

There have been several observational studies that have investigated the question of adverse CV outcomes and TRT use. The results have been inconsistent and conflicting and are insufficient to draw any conclusive relationship between TRT and CV adverse outcomes. In this section, each observational study is evaluated with respect to its strengths and limitations. A descriptive analysis conducted by Lilly is included in this section to further understand the association between TRT and adverse CV outcomes.

**Vigen et al**<sup>2</sup> conducted a retrospective national cohort study of men with low testosterone levels (< 300 ng/dL) who underwent coronary angiography in the Veterans Affairs (VA) system between 2005 and 2011 (publication of this study triggered this FDA review). The primary endpoint was a combined endpoint of time to all-cause mortality or to hospitalization for MI or ischemic stroke. The study included 8,709 men, of which 1,223 patients started testosterone therapy after a median of 531 days (interquartile range, 229 – 894 days) following coronary angiography. The average follow-up was approximately 840 days (27.5 months). The individuals included in the analysis had a high rate of comorbidities, with 20% having a prior history of MI, 50% having diabetes, and more than 80% having CAD. After a median follow-up of 27 months, 748 individuals died, 443 had an MI, and 519 had a stroke. Regarding the combined endpoint of death, MI, and ischemic stroke, the Kaplan-Meier estimated cumulative percentages with events at 1, 2, and 3 years after coronary angiography were 10.1%, 15.4%, and 19.9% in those who did not receive testosterone versus 11.3%, 18.5%, and 25.7% in those who did receive testosterone. The absolute risk difference at 3 years after coronary angiography was 5.8% (95% CI: 1.4%, 13.1%). After adjusting for the presence of CAD, testosterone therapy use as a time-varying covariate was associated with increased risk of adverse outcomes (HR 1.29; 95% CI: 1.04, 1.58;  $P = 0.02$ ).<sup>2</sup> The strengths of the Vigen study are the size of the database and the linkage to laboratory

results. However, this study had a number of limitations and methodologic weaknesses, including:

The estimated risk numbers (i.e., HR = 1.29; 95% CI: 1.04, 1.58) indicate weak evidence of an association.

Detected higher CV risk may be due to patient characteristics rather than treatment (confounding by indication): Vigen used weights to adjust for imbalances in baseline characteristics; however, the 2 cohorts may not have been balanced with respect to underlying CV risk potential (see Section 4.5.3 for data suggestive that worsening hypogonadism is associated with greater CVD and all-cause mortality). On the basis of the mean testosterone levels reported in the study, a number of patients likely remained hypogonadal following treatment and, thus, reflected a subsequent risk of untreated hypogonadal men rather than a cohort treated with TRT.

Outcome definitions were not specific to CV disease: Only "all-cause mortality" was reported, with the cause of death not presented.

The generalizability of the study findings to any TRT patients is questionable since the study population was only composed of hypogonadal men who had undergone coronary angiography.

Importantly, there were errors reported after the original publication. Initially, the authors reported that 1,132 events of MI or stroke were excluded because the events occurred prior to testosterone initiation; later the authors made the correction that the events were excluded due to incomplete angiography results or other reasons for not meeting entry criteria. However, 128 events that should have been included in the no testosterone treatment group were still excluded without a compelling reason. The study's credibility was also questioned by the scientific community and clinicians in letters to JAMA and a call for retraction.<sup>211,250-255</sup> The investigators have twice corrected the online publication, and their conclusions have remained largely unchanged.

**Finkle et al<sup>3</sup>** utilized an electronic health records database containing pharmacy and medical claims to assess whether TRT was associated with an increased risk of acute MI. The study sample was derived from the period 2006 to 2010 and was large, with over

55,000 subjects with a claim for a testosterone prescription. Risk for acute MI was assessed using 2 different approaches: a within-patient pre- and post-treatment design and a comparison of TRT patients with a PDE5 inhibitor (PDE5i) group. In the within-patient design, the authors reported that patients over the age of 65 years had an increased risk (RR = 2.17; 95% CI: 1.27, 3.77) of acute MI in the post-TRT period 90 days after filling a prescription compared with the 1-year baseline period prior to treatment. Subjects age < 65 years with a history of heart disease were reported to have had a higher rate of acute MI following TRT (RR = 2.9; 95% CI: 1.49, 5.62) compared with the baseline period prior to treatment. Notably in this analysis, subjects < 65 years of age with no history of heart disease, which constituted 80% of the entire TRT sample, did not have a statistically higher risk of an acute MI. In addition, most of the significant results were driven by a low number of acute MI cases in the TRT group. A relevant increase in the rate of acute MI was not observed in the PDE5i cohort (RR = 1.08; 95% CI: 0.93, 1.24).

Although the study utilized a large claims database, it had a number of potential limitations, which may have resulted in an exaggeration of the observed risk associated with TRT, including the following:

Questionable study design: 1) Testosterone is prescribed for chronic use, but the investigators limited the follow up to 3 months of therapy. It is unclear whether 3 months might be long enough to capture the outcomes of interest, and there is a lack of analyses of different treatment durations to better characterize and understand the robustness of the findings. 2) It is also questionable whether a PDE5i cohort should be considered to be an appropriate active comparator group—the underlying conditions driving prescribing of these medications are quite different for the TRT and PDE5i cohorts—and the study insufficiently balanced the CV risk factors between the TRT initiator cohorts and the PDE5i initiator cohorts (which had lower CV risk).

Lack of laboratory measurement: Low testosterone has been linked to an increased risk of CV events. The report included results assessing a follow-up time of 90 days post-prescription period. No other follow-up durations were reported, which does not allow for a full assessment of potential benefits and risks of testosterone therapy. It is unclear whether or not this increased risk persisted after initiation of TRT.<sup>228,256-261</sup>

Lacking robustness and small sample size in sub groups: e.g., if 4 cases in patients > 65 years of age were misclassified (e.g., not being incident post-TRT initiation) the post- and pre-increase would not be statistically significant.

The initiation of TRT may have been coincident with worsening comorbidities or diagnoses of other conditions that may have affected monitoring practices, and the study did not adjust for these potential confounders.

Given these study limitations, it is not possible to definitively conclude an association between TRT use and nonfatal acute MI.

To further assess the association of testosterone treatment with the risk of MI, Lilly undertook a preliminary descriptive analysis within the same data source employed by Finkle and colleagues to address whether the findings of increase MI were related to underlying hypogonadism and methodology, or if related to TRT.

The analysis found that an untreated hypogonadal cohort experienced more MIs within 90 days compared with the 1-year baseline period, similar to the pattern in the treated group. The results suggest the findings of MI increases reflect underlying hypogonadism and study methods rather than any causal association with testosterone.

Further, the same data source as Finkle and colleagues was utilized to re-estimate the risk of MI in adult men receiving TRT prescriptions, PDE5i prescriptions, and compared it in hypogonadal men not receiving any TRT. This yet unpublished retrospective, cohort study<sup>206</sup> used the 2006 to 2010 US-based Truven Health MarketScan<sup>®</sup> Research Database (Commercial, Medicare and Multi-State Medicaid data). The primary outcome of hospitalized MI (fatal, nonfatal, or both) was defined by ICD-9 code 410.

Two descriptive analyses were conducted in the current study among 4 cohorts of men: 1) TRT only-treated men versus PDE5i-treated men and 2) TRT-treated men versus untreated hypogonadal men. The summary study<sup>206</sup> findings are as follows:

The first descriptive analysis demonstrated a numerical increase in the observed MI incidence rate among men receiving TRT during the post-index period compared with the pre-index period (Table 17). Specifically, the unadjusted analysis showed an increase in the observed MI incidence rate for the TRT only cohort during the 90-day post-index period (5.64 [95% CI: 4.65, 6.63] per 1,000 PY) versus the 365-day pre-index period (4.80 [95% CI: 4.38, 5.22] per 1,000 PY), especially among elderly patients (> 65 years). By contrast, an increase trend in the MI incidence rate was not found during the 90-day post-index period among men administered PDE5i.

In the second descriptive analysis, for the treated cohort, the increase in the observed MI incidence rate during the 90-day post-index period (5.61 [95% CI: 4.76, 6.45] per 1,000 PY) versus the 365-day pre-index period (4.59 [95% CI: 4.24, 4.95] per 1,000 PY) was similar to the increase observed among untreated hypogonadal men in the 90-day post-index period (6.57 [95% CI: 5.40, 7.73] per 1,000 PY) versus the 365-day pre-index period (4.48 [95% CI: 4.03, 4.92] per 1,000 PY) (Table 18). Overall, a similar numerical increase in the observed MI incidence rate was demonstrated in both treated and untreated cohorts during the first 90 days after they obtained prescriptions for TRT and in the cohort of untreated hypogonadal men during the first 90 days after a randomly assigned hypogonadism diagnosis date.

Further sensitivity analyses showed that the conditional probability of a MI event in 30-day time windows during the 1-year pre-index period was similar in TRT-treated men compared with untreated hypogonadal men (Figure 6). The lack of apparent differences in the observed incidence of MI between TRT-treated men and untreated hypogonadal men was also upheld in the post-index period, especially among men < 65 years. Although similar results were also observed for men > 65 years, there was greater variability in the MI incidence rates in this age group.



**Table 17. Rates of MI per 1,000 PY in All Men, Men Aged ≤ 65 Years, and Men Aged > 65 Years in Pre- and Post-Prescription Interval for Initial Testosterone Replacement Therapy Versus PDE5i**

Unadjusted Analysis	Men with TRT prescription*			Men with PDE5i prescription*		
	All ages	Age < 65 years	Age > 65 years	All ages	Age < 65 years	Age > 65 years
Subjects (N)	105,815	94,570	11,245	359,321	310,243	49,078
<b>Pre-prescription (pre-index): 365 days</b>						
Cases, n	508	402	106	1656	1354	302
Rate per 1,000 PY	4.80	4.25	9.43	4.61	4.36	6.15
95% CI	4.38, 5.22	3.84, 4.67	7.63, 11.22	4.39, 4.83	4.13, 4.60	5.46, 6.85
<b>Post-prescription (post-index): 90 days</b>						
Cases, n	125	91	34	379	298	81
Rate per 1,000 PY	5.64	4.61	14.17	4.82	4.42	7.27
95% CI	4.65, 6.63	3.66, 5.56	9.41, 18.94	4.34, 5.31	3.92, 4.92	5.69, 8.86

CI = confidence interval; N = number of subjects; PDE5i = phosphodiesterase type 5 inhibitor; PY = person years; TRT = testosterone replacement therapy.

\*Men taking a concomitant testosterone product and PDE5i were excluded.

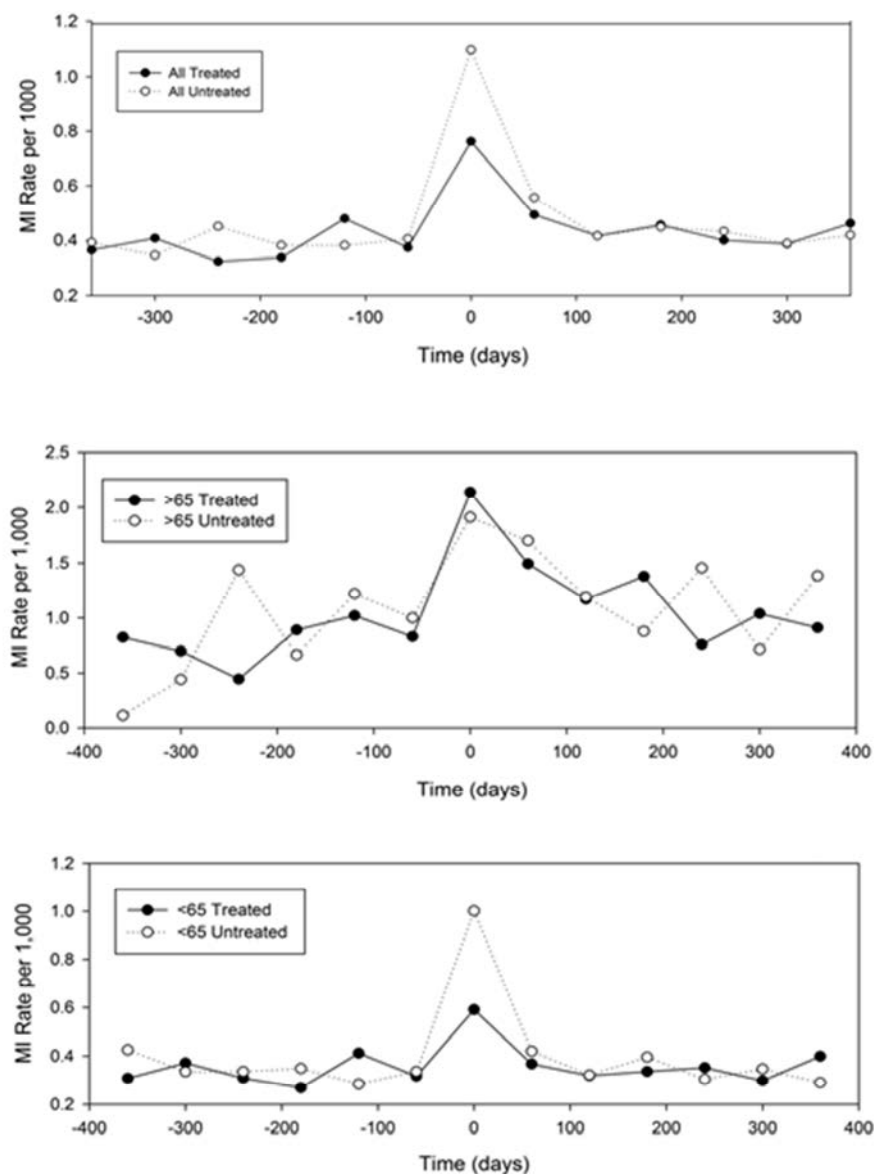
**Table 18. Rates of MI per 1,000 PY Pre- and Post-Index Intervals for Initial Testosterone Replacement Therapy Prescription or First Randomly Assigned Date of Diagnosis with Hypogonadism Without a Testosterone Replacement Therapy Prescription**

	Men with TRT prescription*			Men with no TRT prescription*		
	All ages	Age < 65 years	Age > 65 years	All ages	Age < 65 years	Age > 65 years
Subjects (N)	142,358	126,575	15,783	86,643	77,579	9,064
<b>Pre-prescription (pre-index): 365 days</b>						
Cases, n	654	511	143	388	305	83
Rate per 1,000 PY	4.59	4.04	9.06	4.48	3.93	9.16
95% CI	4.24, 4.95	3.69, 4.39	7.58, 10.55	4.03, 4.92	3.49, 4.37	7.19, 11.13
<b>Post-prescription (post-index): 90 days</b>						
Cases, n	169	124	45	122	93	29
Rate per 1,000 PY	5.61	4.64	13.29	6.57	5.61	14.55
95% CI	4.76, 6.45	3.82, 5.45	9.41, 17.17	5.40, 7.73	4.47, 6.75	9.26, 19.85

CI = confidence interval; N = number of subjects; PDE5i = phosphodiesterase type 5 inhibitor; PY = person years; TRT = testosterone replacement therapy.

\*Men taking a PDE5i were not excluded.

**Figure 6. Myocardial Risk Rate 1 Year Prior to and 1 Year After Index Date**



MI = myocardial infarction; PDE5i = phosphodiesterase type 5 inhibitor; TRT = testosterone replacement therapy  
Conditional probability of a myocardial event rate in TRT-treated men and untreated hypogonadal men (men taking a PDE5i were not excluded from either cohort) 1 year prior to and 1 year post index date using 60-day window intervals: 1A) all ages combined, 1B) > 65 years, 1C) < 65 years. Index date defined as the first prescription of TRT, first prescription of PDE5i, or first randomly assigned hypogonadism diagnosis date. 0 = index date.

In summary, the descriptive analyses raised the concern that the recent findings of Finkle and colleagues should be questioned. If rates of MI rise similarly in men treated with TRT and in hypogonadal men not receiving TRT, it is difficult to assign causality to TRT using observational data. Rather, consistent with the epidemiologic literature, hypogonadism itself may increase the risk of MI, or the observed increased MI risk shortly following TRT may in fact be a fallacy based on inappropriate study design.

**Baillargeon et al<sup>262</sup>** recently published an observational study which examined the risk of MI in a population-based cohort of older men (> 66 years) receiving intramuscular testosterone from a Medicare claims database. TRT was not associated with an increased risk of MI (adjusted HR = 0.84; 95% CI: 0.69, 1.02). Additionally, as noted below, testosterone use was modestly protective against MI in men with high MI risk.<sup>262</sup>

Patients who received testosterone therapy (n = 6,355) were matched 1:3 to non-users (n = 19,065) on a prognostic index score for MI. The period of observation was from 1997 through 2005. Cox proportional hazards regression was used to quantify the risk contribution of TRT while adjusting for possible confounding factors. The results indicate that men who received testosterone therapy were at no increased risk for MI (adjusted HR = 0.86; 95% CI: 0.71, 1.05). Statistical adjustments were made for observed differences in education, comorbidity score (e.g., Elixhauser score), and indications for TRT. No adjustments were possible for CV preventive medications because such information was not available in the data set. For patients with the highest assumed risk of MI (i.e., highest quartile of the prognostic score), TRT was associated with a reduced risk of MI (adjusted HR = 0.69; 95% CI: 0.53, 0.92). There were no statistically elevated risk numbers observed for patients within the remaining risk groups: first quartile 1.20 (0.88, 1.67), second 0.94 (0.69, 1.30), and third 0.78 (0.59, 1.01). Of note, the estimated risk numbers for TRT do consistently decrease with an increased MI risk score pointing towards an inverse correlation. The strengths in this study are the large number of patients, over 25,000 men in both of the 2 study groups combined, the fairly long period of follow-up (each group could be followed for more than 3 years), and

the approach to matching patients on a prognostic score for MI appears sound. Some weaknesses of this study include:

The Cox proportional hazards model contained variables for TRT treatment and a variable for each of the major complaints associated with TRT. Compared with the no-treatment group, men who received TRT had about a 2-fold increase for having fatigue as a symptom (29.8% to 14.3%), a 100-fold increase for hypogonadism (41.6% to 0.4%), a 3.8-fold increase for osteoporosis (6.5% to 1.7%), and a 15-fold increase for sexual dysfunction (56.9% to 3.7%). Including each of these indications and including TRT treatment in the Cox model may have introduced multicollinearity (i.e., very strong correlation between more than 2 predictive variables) into the model. No adjustment for CV preventive medications was possible. Yet, the likelihood that such an adjustment would have resulted in the TRT group having a statistically significantly higher risk of MI seems highly unlikely. Important information that would contribute to the interpretation of the results was not included. For example, the number of MIs—overall or per group—is not reported. Such information can be useful in determining the unadjusted rate of MI to the adjusted rate. Comparing the unadjusted risk to the adjusted risk may provide insight about the influence that multicollinearity may have had on the adjusted analysis.

Other studies below also may be relevant to the question of whether testosterone can be linked to increased CV risk, including:

**Shores et al<sup>232</sup>** conducted a retrospective, observational study (N = 1,031) using clinical data from 7 VA medical centers on middle aged (< 40 years of age) men with low testosterone levels. Testosterone treatment was associated with decreased mortality compared with no testosterone treatment. The mortality in testosterone-treated men was 10.3% compared with 20.7% in untreated men with a mortality rate of 3.4 deaths per 100 person years (PY) for testosterone-treated men and 5.7 deaths per 100 PY in men not treated with testosterone. After multivariable adjustment including age, BMI, testosterone level, medical morbidity, diabetes, and CHD, testosterone-treated men had a 39%

reduction in mortality risk (HR = 0.61; 95% CI: 0.42, 0.88), compared with untreated men. No significant effect modification was found by age, diabetes, or CHD.<sup>232</sup>

**Brooke et al**<sup>263</sup> performed a long-term retrospective audit to evaluate TRT's safety in 401 (47.4% T2DM, 34.0% CVD) hypogonadal men (age  $58.7 \pm 14.3$  years) receiving TRT (84% testosterone gels) with a mean follow-up of 5.41 years. The BMI, waist circumference, blood pressure, hemoglobin, hematocrit, lipid profile, liver function, testosterone, estradiol, and PSA levels were monitored at 3, 6, and 12 months and yearly thereafter. Hospital admissions, major adverse CV events (MACEs), mortalities, and prostate-related outcomes were recorded. Over the course of the study, 24 MACEs (4 MI, 8 angina, 5 transient ischemic attacks, 2 CVAs, 4 coronary artery bypass grafts, 1 congestive cardiac failure), 54 hospital admissions, and 2 deaths were identified, which were no higher than expected in a population with similar comorbidities as the Brooke cohort. The authors conclude that in clinical practice, TRT may have beneficial effects on CV risk factors including circulating lipid and cholesterol levels. The authors noted this is the largest and most comprehensive study of TRT safety to date (2012), representing over 1,642 patient years of TRT.<sup>263</sup>

**Muraleedharan et al**<sup>246</sup> found that in hypogonadal men with T2DM, absence of TRT was associated with lower survival (multivariate-adjusted HR for decreased survival in the untreated group was 2.3; 95% CI: 1.3, 3.9). They concluded that low testosterone levels predicted an increase in all-cause mortality during long term follow-up, and testosterone replacement may improve survival in hypogonadal men with T2DM.

#### **4.7 Evaluation of Testosterone Replacement Therapy and Cardiovascular Risk Factors**

Multiple studies have shown beneficial or neutral effects of TRT on LDL cholesterol, triglycerides, and total cholesterol levels.<sup>76,225-227,260,263,264</sup>

Studies are mixed on the relationship between TRT and HDL cholesterol,<sup>256,257</sup> with some showing an increased or neutral effect,<sup>175,226,260,261</sup> and others showing a decreased effect.<sup>225,260,265</sup>

The data indicate that the impact of TRT on HDL cholesterol is both route of administration-specific, as well as dose-specific.<sup>264</sup>

The studies reporting effects of TRT on lipids, LDL cholesterol, HDL cholesterol, triglycerides, and cholesterol are summarized in [Table 19](#) (additional information regarding these studies is provided in [Appendix C](#)).

**Table 19. Published Meta-Analyses of Studies Examining Testosterone Replacement Therapy and Risk Factors for Cardiovascular Disease**

Endpoint – Units	Measure	Estimated Magnitude of Measure (95% CI) <sup>a</sup>	Source	N
<b>Blood Pressure</b>				
Blood Pressure, Systolic – mmHg	Mean Difference	0.8 (–4.0, 5.0)	Haddad et al 2007 <sup>228</sup>	NA
Blood Pressure, Diastolic – mmHg	Mean Difference	2 (–2.0, 6.0)	Haddad et al 2007 <sup>228</sup>	NA
<b>Total Cholesterol</b>	--			
<i>Total Cholesterol – mmol/L</i>	<i>Mean Difference</i>	<i>–0.23 (–0.37, –0.10)</i>	<i>Isidori et al 2005<sup>76</sup></i>	<i>NA</i>
<i>Total Cholesterol – mmol/L (in men with baseline testosterone &lt; 10 nmol/L)</i>	<i>Mean Difference</i>	<i>–0.42 (–0.65, –0.19)</i>	<i>Isidori et al 2005<sup>76</sup></i>	<i>NA</i>
<i>Total Cholesterol – mmol/L (in men with baseline testosterone ≥ 10 nmol/L)</i>	<i>Mean Difference</i>	<i>–0.14 (–0.30, –0.03)</i>	<i>Isidori et al 2005<sup>76</sup></i>	<i>NA</i>
Total Cholesterol – mmol/L (in men with low testosterone < 10.4 nmol/L)	Mean Difference	–0.22 (–0.71, 0.27)	Haddad et al 2007 <sup>228</sup>	119
<i>Total Cholesterol – mmol/L (in men with low-normal or normal testosterone &gt; 10.4 nmol/L)</i>	<i>Mean Difference</i>	<i>–0.47 (–0.77, –0.17)</i>	<i>Haddad et al 2007<sup>228</sup></i>	<i>119</i>
Total Cholesterol – mmol/L (in men with chronic disease)	Mean Difference	–0.15 (–0.69, 0.38)	Haddad et al 2007 <sup>228</sup>	119
Total Cholesterol	Mean Difference	–1.39 (–6.41, 3.63)	Fernández-Balsells et al 2010 <sup>225</sup>	NA

See notes at end of table.

**Table 19. Published Meta-Analyses of Studies Examining Testosterone Replacement Therapy and Risk Factors for CV Disease (Continued)**

Endpoint – Units	Measure	Estimated Magnitude of Measure (95% CI) <sup>a</sup>	Source	N
<b>HDL Cholesterol</b>				
HDL Cholesterol – mmol/L	Mean Difference	–0.04 (–0.11, 0.03)	Isidori et al 2005 <sup>76</sup>	1083
HDL Cholesterol – mmol/L (in men with baseline testosterone < 10 nmol/L)	Mean Difference	–0.01 (–0.05, 0.08)	Isidori et al 2005 <sup>76</sup>	NA
HDL Cholesterol – mmol/L (in men with baseline testosterone ≥ 10 nmol/L)	Mean Difference	–0.09 (–0.17, –0.003)	Isidori et al 2005 <sup>76</sup>	NA
HDL Cholesterol – mmol/L (in men with low testosterone < 10.4 nmol/L)	Mean Difference	–0.04 (–0.39, 0.30)	Haddad et al 2007 <sup>228</sup>	119
HDL Cholesterol – mmol/L (in men with low-normal or normal testosterone ≥ 10.4 nmol/L)	Mean Difference	–0.21 (–0.43, 0.01)	Haddad et al 2007 <sup>228</sup>	119
<i>HDL Cholesterol – mmol/L (in men with chronic disease)</i>	<i>Mean Difference</i>	<i>–0.73 (–1.29, –0.18)</i>	<i>Haddad et al 2007<sup>228</sup></i>	<i>119</i>
<i>HDL Cholesterol</i>	<i>Relative Risk</i>	<i>–0.49 (–0.85, –0.13)</i>	<i>Fernández-Balsells et al 2010<sup>225</sup></i>	<i>NA</i>

See notes at end of table.



**Table 19. Published Meta-Analyses of Studies Examining Testosterone Replacement Therapy and Risk Factors for CV Disease (Continued)**

Endpoint – Units	Measure	Estimated Magnitude of Measure (95% CI) <sup>a</sup>	Source	N
<b>LDL Cholesterol</b>				
LDL Cholesterol – mmol/L	Mean Difference	–0.12 (–0.34, 0.09)	Isidori et al 2005 <sup>76</sup>	NA
LDL Cholesterol – mmol/L (in men with baseline testosterone <10 nmol/L)	Mean Difference	–0.33 (–0.80, 0.14)	Isidori et al 2005 <sup>76</sup>	NA
LDL Cholesterol – mmol/L (in men with baseline testosterone ≥ 10 nmol/L)	Mean Difference	0.02 (–0.15, 0.18)	Isidori et al 2005 <sup>76</sup>	NA
LDL Cholesterol – mmol/L (in men with low testosterone <10.4 nmol/L)	Mean Difference	0.06 (–0.30, 0.42)	Haddad et al 2007 <sup>228</sup>	107
LDL Cholesterol – mmol/L (in men with low-normal or normal testosterone ≥10.4 nmol/L)	Mean Difference	–0.25 (–0.57, 0.08)	Haddad et al 2007 <sup>228</sup>	119
LDL Cholesterol – mmol/L (in men with chronic disease)	Mean Difference	0.16 (–0.56, 0.88)	Haddad et al 2007 <sup>228</sup>	119
LDL Cholesterol	Mean Difference	0.34 (–4.53, 5.21)	Fernández-Balsells et al 2010 <sup>225</sup>	NA

See notes at end of table.

**Table 19. Published Meta-Analyses of Studies Examining Testosterone Replacement Therapy and Risk Factors for CV Disease (Continued)**

Endpoint – Units	Measure	Estimated Magnitude of Measure (95% CI) <sup>a</sup>	Source	N
<b>Triglycerides</b>				
Triglycerides – mmol/L (in men with low testosterone < 10.4 nmol/L)	Mean Difference	–0.27 (–0.61, 0.08)	Haddad et al 2007 <sup>228</sup>	119
Triglycerides – mmol/L (in men with low-normal or normal testosterone)	Mean Difference	0.15 (–0.20, 0.50)	Haddad et al 2007 <sup>228</sup>	337
Triglycerides – mmol/L (in men with chronic disease)	Mean Difference	–0.19 (–0.90, 0.53)	Haddad et al 2007 <sup>228</sup>	119
<i>Triglycerides – mmol/L (in men with metabolic syndrome)</i>	<i>Mean Difference</i>	<i>–0.40 (–0.66, –0.14)</i>	<i>Corona et al 2013<sup>249</sup></i>	<i>483</i>
<i>Triglycerides – mmol/L (in men with type 2 diabetes)</i>	<i>Mean Difference</i>	<i>–0.60 (–0.83, –0.37)</i>	<i>Corona et al 2013<sup>249</sup></i>	<i>263</i>
<b>Diabetes</b>				
New Onset Diabetes	Relative Risk	0.67 (0.12, 3.67)	Fernández-Balsells et al 2010 <sup>225</sup>	152
<i>Fasting Glucose (in men with type 2 diabetes)</i>	<i>Mean Difference (%)</i>	<i>–0.62 (–1.0, –0.24)</i>	<i>Corona et al 2013<sup>249</sup></i>	<i>263</i>
<b>Hematocrit</b>				
<i>Hematocrit &gt;50%</i>	<i>Odds Ratio</i>	<i>3.69 (1.82, 7.51)</i>	<i>Calof 2005<sup>226</sup></i>	<i>1070</i>
<i>Hematocrit &gt;52%</i>	<i>Relative Risk</i>	<i>3.15 (1.56, 6.35)</i>	<i>Fernández-Balsells et al 2010<sup>225</sup></i>	<i>NA</i>

CI = confidence interval; HDL = high-density lipoprotein; LDL = low-density lipoprotein; N = number of pooled patients; NA = not available; NS = nonsignificant

a. Values presented in italic boldface type achieved statistical significance.

## 4.8 Summary

Global and US epidemiological data indicate that hypogonadal men may have a higher prevalence and incidence of CV-related events compared with the general male population.<sup>1,208,226,232,244</sup>

A small number of observational studies in the scientific literature recently have raised a concern about the long-term effects of TRT. Two observational studies,<sup>2,3</sup> 1 meta-analysis (that included 27 heterogeneous clinical trials),<sup>205</sup> and 1 RCT<sup>115</sup> report associations between CV events and testosterone therapy. However, a number of important issues have been raised regarding these analyses: Vigen et al<sup>2</sup> reported a 30% higher risk of stroke, heart attack, and death in hypogonadal men prescribed testosterone versus hypogonadal men not prescribed testosterone; however, the limited magnitude, lack of consistency, and confounding factors likely influencing patient treatment status are insufficient for any conclusive relationship between TRT and CV adverse outcomes to be drawn. The study by Finkle et al<sup>3</sup> reported a 2- to 3-fold higher risk of heart attack in older men > 65 years of age, and in younger men with preexisting CVD, 90 days after filling a prescription compared with a 1-year baseline period. However, the study lacked robustness due to the small sample sizes in the subgroup analyses, and no adjustment in the pre/post comparison was performed for potential confounding factors. Preliminary descriptive analyses, performed by a TRT Sponsor, using the same database used by Finkle et al<sup>3</sup> indicate that the pattern of higher MIs reported in the Finkle study is more likely related to underlying hypogonadism and study methods than to TRT. Importantly, unadjusted analyses did not confirm the conclusion that testosterone was associated with a higher incidence of MI, because a similar pattern of higher incidence of MI was also seen in hypogonadal untreated patients. These results were replicated upon evaluating multiple time-intervals (baseline, 90 days post index and/or at refill, 180 days or through the end of enrollment). The results did confirm the higher incidence of MI associated with age. Finally, one relatively small clinical trial employing a high starting dose of testosterone followed by rapid titration in elderly frail men (TOM trial<sup>115</sup>) was the only clinical trial that showed statistically significant CV risk among the 27 studies included in

meta-analyses by Xu et al.<sup>205</sup> The nonspecific, broad CV-related events and outcomes were not predefined and in the TOM trial were retrospectively ascertained. Furthermore, the exclusion of a number of relevant studies<sup>224,266-271</sup> from the Xu et al meta-analysis is raises concerns about the methodology.

Much of the available data do not suggest an association between MACE and TRT. Albeit limited in design and size to detect MACE or broad CV events, the majority of RCTs, meta-analyses, and observational studies have not shown the consistency or magnitude of effects to support a causal relationship between MACE and TRT. Furthermore, there are limited data from meta-analyses and long-term treatment, which show improvements in some CV risk outcomes.

Contrary to the results seen in the TOM trial, a randomized placebo-controlled study by Srinivas-Shankar et al<sup>114</sup> did not demonstrate an increased risk of CV-related events in a population of men similar, albeit less frail, to those in the TOM trial. A study by Muraleedharan et al<sup>246</sup> in men with T2DM (who are known to have a high prevalence of both testosterone deficiency and CV disease) demonstrated increased mortality in the low testosterone group compared with the group with normal testosterone levels and concluded that "low testosterone levels predict an increase in all-cause mortality during long-term follow-up. Testosterone replacement may improve survival in hypogonadal men with T2DM." Additionally, the authors of a long-term retrospective audit to evaluate TRT safety in 401 hypogonadal men concluded that in clinical practice TRT has beneficial effects on CV risk factors including circulating lipid and cholesterol levels.<sup>263</sup> However, as is expected of observational studies, this study also had limitations, and the results should be considered in this context. Furthermore, the most recently published retrospective observational study by Baillargeon et al<sup>262</sup> examined the risk of MI in a population-based cohort of older men (> 66 years) receiving intramuscular testosterone in the Medicare claims database and concluded that older men treated with intramuscular testosterone did not have an increased risk of MI (adjusted HR = 0.84; 95% CI = 0.69, 1.02). Additionally, testosterone use was modestly protective against MI in men with high MI risk. Baillargeon et al speculate that the cardio-protective effect of

testosterone "among men in the highest MI prognostic group reflects a process whereby testosterone reduces peripheral vascular resistance, thereby reducing stress on the heart among those who have some degree of CAD."<sup>262</sup>

Finally, there is evidence that underlying hypogonadism and comorbid disease severity may be mediating differences in CV event rates in observational studies; 2 observational studies in different external databases<sup>204</sup> found that the prevalence of baseline CV comorbidities is higher among hypogonadal men prior to receiving TRT compared with hypogonadal men who remain untreated. These findings suggest that testosterone users may have greater CV morbidity in general and/or there may be systematic bias in prescribing. This is consistent with evidence that low testosterone is associated with metabolic risk factors that are also risk factors for CV events and data showing higher incidence of MI within 90 days among untreated patients with hypogonadism. These data support the idea that hypogonadal men may already be at high risk for CV events when they initiate treatment.

In summary, based upon the totality of data, no conclusive evidence exists to support an association between TRT and an increased risk of CV-related events including stroke, MI, or CV death. However, the TRT Sponsors recognize that continued active surveillance is required given the questions raised, particularly in certain subpopulations, such as elderly men and/or patients with preexisting CV disease. Patients seeking TRT should be provided preventive CV standard of care similar to patients not seeking TRT and in adherence with general CV preventive care guidelines.<sup>272</sup>

## **5.0 Drug Utilization**

### **5.1 Drug Utilization Introduction**

The intent of this section is to summarize data regarding trends in prescribing patterns of testosterone products, as well as characteristics of patients receiving TRT, such as demographics, reasons for use, prevalence of laboratory testing for testosterone, and length of treatment. Given time considerations for preparing this briefing book, available

information for this review includes literature and/or ad hoc analyses of prescribing patterns using existing data sources.

## **5.2 Background: Prevalence of Hypogonadism and Common Comorbid Conditions**

The prevalence of hypogonadism and comorbid conditions that are associated with hypogonadism are described in Sections [3.2.2](#) and [3.2.3](#).

As discussed in Section [3.2.2](#), estimates of prevalence for symptomatic hypogonadism vary from 2.1% to 25.5%, with a consistent trend toward an increased prevalence with age. Also, Section [3.2.3](#) summarizes a number of common comorbid conditions that are associated with hypogonadism.

## **5.3 Prescription Trends over Time for Testosterone Products**

The TRT Sponsors assessed prescription trends for testosterone products over time, by evaluating available literature and via a data analysis conducted by AbbVie.

The data generally show consistent increases in the monthly number of prescriptions from January 2000 to July 2014, from just over 55,000 in 2000 to over 546,000 in 2014, an approximate 8.8-fold increase in the number of prescriptions during this period of observation.

Relevant literature includes the studies described below:

In a study by Layton et al, 410,019 men in the US and 6,858 men in the UK were identified who initiated TRT from 2000 – 2011. The study showed that, over this time period, the rates of TRT use quadrupled in the cohort of US men as compared with the cohort of UK men. These results were observed in the context of comparable increases in testing rates for both cohorts of men.<sup>283</sup>

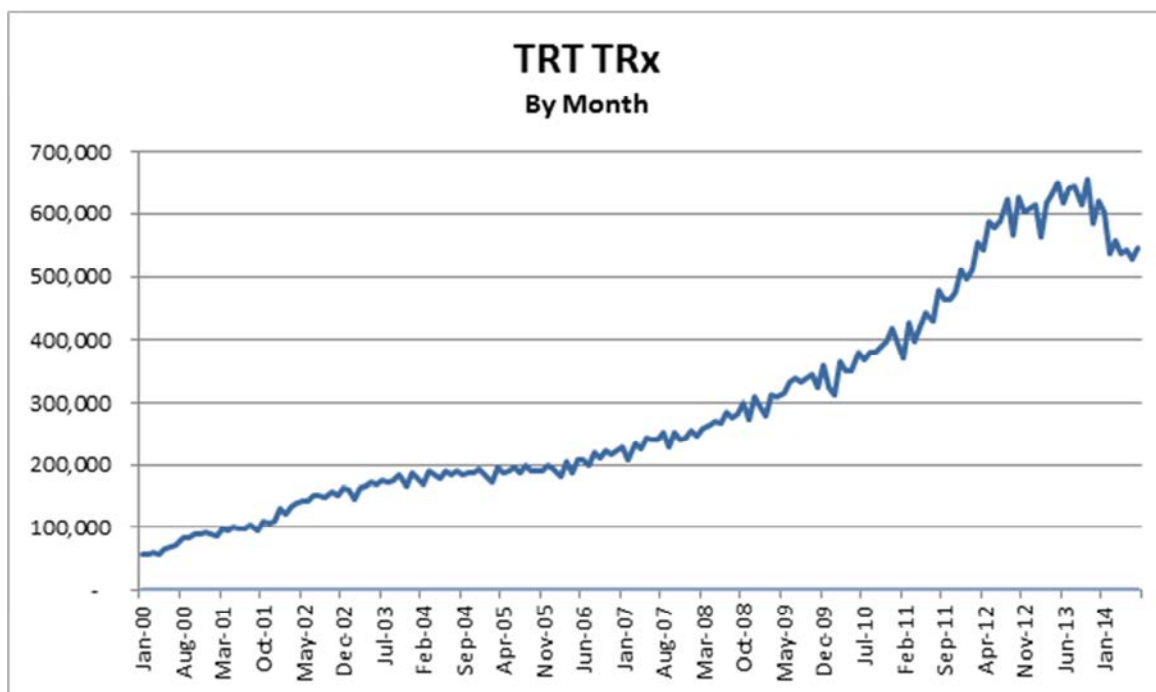
Testosterone prescribing patterns in the US over the past decade were examined in men 40 years of age or older using data from the ClinformaticsDataMart (CDM).<sup>273</sup> This study showed a more than 3-fold increase in the percentage of men receiving TRT from 0.81% in 2001 to 2.91% in 2011.

The analysis of the IMS and SHA IDV databases is reported below:

To further assess prescribing trends over time, AbbVie performed an analysis on the IMS National Prescription Audit™ (NPA) (see [Appendix D](#) for a description of NPA) and the SHA IDV databases. The IMS NPA data for the period between January 2009 and May 2014 was selected, as it was readily available and facilitated the assessment of recent trends of TRT use and prescribing patterns. First, the NPA was used to identify trends in the number of prescriptions filled for TRT over time followed by an analysis of prescribing patterns by physician specialties associated with these prescriptions.

The number of prescriptions for TRT in the IMS NPA database increased from just over 55,000 to over 546,000 between January 2000 and July 2014 ([Figure 7](#)), an 8.8-fold increase over this period. However, monthly fluctuations occur, and the number of prescriptions in July 2014 was lower than from March 2012 through about March 2014.

**Figure 7. Volume of Prescriptions by Month, January 2000 to July 2014**



Data source IMS NPA [Projected TRx]; TRx = testosterone prescriptions

Potential reasons for recent increased use patterns have been considered and may be attributed to a number of factors, including the following:

- New guidelines covering the recognition, diagnosis and treatment of hypogonadism (e.g., Endocrine Society 2001, 2006, and 2010, International Society for the Study of the Aging Male/International Society of Andrology 2009);

- Approval of a number of different formulations of TRT from 2000 through 2014, which provided for additional options;

- TRT Sponsors' product promotional activities and non-product-specific disease awareness activities directed at health care providers, patients, and consumers, consistent with FDA requirements and guidelines, leading to heightened awareness of hypogonadism, the signs and symptoms of hypogonadism, and available treatment options;



Non-sponsors' promotion of testosterone-boosting dietary supplements, which may also lead men seeking additional information to their physicians for full information regarding treatment options;

Proliferation of specialty "Low Testosterone" Centers offering targeted testosterone replacement services; and

Broadening knowledge regarding safety of TRT (e.g., Marks et al 2006<sup>276</sup> showing that intraprostatic DHT and testosterone concentrations do not change in hypogonadal men before and during replacement therapy).

#### **5.4 Prescribing Patterns by Physician Specialty**

The TRT Sponsors assessed prescribing patterns by physician specialty, over time, by evaluating available literature and via a data analysis conducted by AbbVie.

Recent data show that the majority of prescriptions (approximately 60%) are provided by primary care physicians (PCP). Endocrinologists and urologists combined accounted for approximately 22% of the prescriptions.

Relevant literature includes the studies described below:

Although the published data on this topic is sparse, Kaltenboeck et al found that PCPs accounted for nearly 50% of the hypogonadism diagnoses.<sup>277,278</sup>

The analysis of the IMS database is reported below:

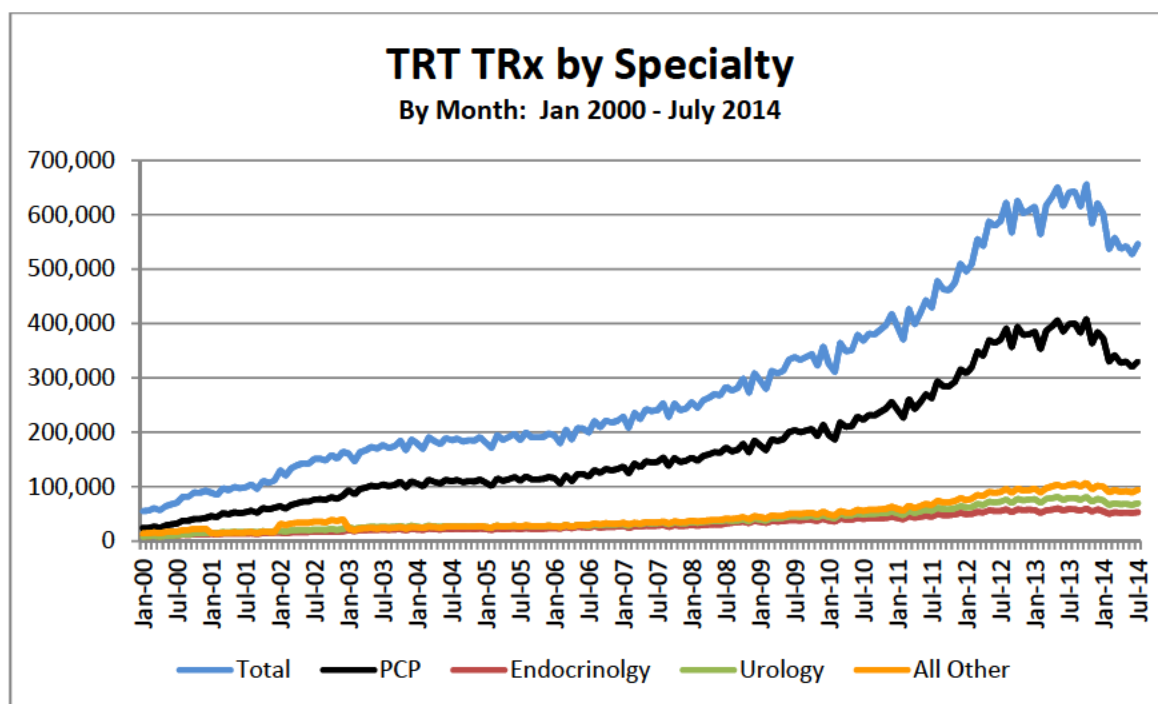
To further evaluate prescriber patterns by physicians AbbVie performed an analysis on the IMS NPA data. The results of this analysis are presented below (Figure 8), which shows the monthly frequency of TRT prescribing by physician specialty.

Consistent with Kaltenboeck et al (2012), PCPs accounted for most of the monthly number of TRT prescriptions from January 2000 to July 2014. The monthly number of prescriptions attributed to PCPs increased 12.6-fold from 24,135 in January 2000 to 329,918 in July 2014. PCPs, then, accounted for

43.7% of all TRT prescriptions in January 2000, but 60.4% of the TRT prescriptions in July 2014.

The number of TRT prescriptions by endocrinologists and urologists increased over the period of observation by 7.3-fold (from 8,327 to 69,133) and 5.1-fold (from 8,722 to 52,901), respectively. For July 2014, endocrinologists and urologists combined accounted for approximately 22% of the monthly prescriptions. In January 2000, endocrinologists and urologists contributed to 30.8% of the total monthly prescriptions. See [Appendix E](#), which provides representative information on prescribers by specialty from an analysis of IMS data from 2009 through May 2014.

**Figure 8. Number of Prescriptions by Specialty**



TRT = testosterone replacement therapy; TRx = testosterone prescriptions; PCP = primary care physicians  
Data source: IMS NPA [Projected TRx]  
PCP totals include Family Practice, General Practice, Internal Medicine, and Osteopathic Medicine.

## 5.5 Age Distribution of Patients Receiving Testosterone Replacement Therapy

The TRT Sponsors assessed the age distribution of patients receiving testosterone therapy, by evaluating available literature and via a data analysis conducted by AbbVie.

The data show that the age group of men 45 to 64 years old receives the highest number of prescriptions (approximately 60%), a trend that has not changed in the past few years. Men younger than 45 years represent approximately 19% of prescriptions, while men older than 65 years represent approximately 21% of prescriptions.

Relevant literature includes the studies described below:

The study by Baillargeon et al evaluated men taking TRT who were > 40 years of age.<sup>273</sup> Of these men, 73% and 27% fell into the age ranges of 40 – 59 years old and > 60 years old, respectively. Over the 10-year period evaluated in this study, a cumulative increase of 40,441 men using TRT was observed. Of this increase, 72% and 28% were attributable to the 40 – 59 year and > 60 year age groups, respectively.

In the Ingenix Employer Solutions Claims Database, Kaltenboeck et al (2012) reported a mean age of 51 years (SD = 7; range 35 to 64) in men with 2 medical claims on different dates with a diagnosis of hypogonadism or 1 medical claim for a hypogonadism diagnosis and 1 medical or pharmacy claim for testosterone.<sup>277</sup>

In the Thomson Reuters MarketScan® Database, Schoenfeld et al (2013) reported that more than half (54.26%) of the men with one or more claims for TRT were between 50 and 64 years of age.<sup>278</sup>

The analysis of the SHA IDV database is reported below:

Similar trends for age distribution were found in nonpublished results of the analysis performed by AbbVie on the Source Health Care Analytics Integrated Dataverse (SHA IDV) database for the period between January 2009 and May 2014. The annual distribution of prescriptions filled between January 2009 and May 2014 is presented in [Table 20](#) by patient age group.

In the SHA IDV database prescriptions for each age group increased over time through 2013. The age group 45 – 64 years accounts for the largest number (about 60%) of prescriptions.

For 2009 and 2013, prescriptions for TRT for men 45 – 64 years of age made up 57% and 67%, respectively. In these same years, TRT prescriptions for men younger than 45 years were 12% and 18%, respectively; while TRT prescriptions for men older than 65 years were 31% and 21%, respectively.

The largest percentage increases between 2009 and 2013 were in the younger age categories as follows: 230% for men < 25 years of age, 282% for men 26 – 34 years of age, and 262% for men 35 – 44 years of age. Although the number of prescriptions for each of these age groups more than tripled between 2009 and 2013, these 3 groups combined only represent approximately 12% and 18% of the total number of TRT prescriptions filled in 2009 and 2013, respectively.

**Table 20. Number of Testosterone Replacement Therapy Prescriptions by Patient Age (2009 to May 2014)**

Age, yrs	2009	2010	2011	2012	2013	2014 YTD
< 25	15,124 (0.6%)	19,336 (0.7%)	27,773 (0.7%)	37,996 (0.7%)	49,897 (0.9%)	23,915 (1.1%)
26 – 34	49,373 (2.0%)	63,723 (2.2%)	97,923 (2.5%)	147,697 (2.9%)	188,739 (3.4%)	85,818 (4.1%)
35 – 44	217,815 (9.0%)	284,072 (9.9%)	429,511 (11.1%)	640,076 (12.6%)	788,504 (14.1%)	331,810 (15.9%)
45 – 54	579,699 (23.9%)	726,187 (25.3%)	1,047,280 (26.9%)	1,448,439 (28.5%)	1,656,641 (29.6%)	634,818 (30.3%)
55 – 64	810,676 (33.4%)	958,374 (33.4%)	1,266,599 (32.6%)	1,612,768 (31.7%)	1,736,868 (31.1%)	622,721 (29.8%)
65 – 74	541,798 (22.3%)	599,739 (20.9%)	757,873 (19.5%)	908,099 (17.9%)	904,732 (16.2%)	308,748 (14.8%)
> 75	211,566 (8.7%)	219,073 (7.6%)	259,939 (6.7%)	287,115 (5.6%)	263,781 (4.7%)	84,600 (4.0%)
Total	2,426,051	2,870,504	3,886,898	5,082,190	5,589,162	2,092,430

Data source: SHA's Integrated Dataverse, nonprojected claims counts.

2014 YTD = Year to date from January to May 2014

## **5.6 Characteristics of Patients Receiving Testosterone Replacement Therapy**

The TRT Sponsors evaluated relevant literature characterizing etiology of hypogonadism and or signs and symptoms of patients treated with TRT.

In terms of etiology of hypogonadism, there is limited published information about the use of TRT.

Relevant literature includes the studies described below:

Steidle et al (2003) in a clinical trial of Testim,<sup>17</sup> reported that 9% of men had a primary cause of hypogonadism and 91% had a secondary cause; of those, 64.1% was attributed to aging and 27.0% to normogonadotrophic hypogonadism.<sup>17</sup>

Clinical trial data for AndroGel 1% (1999), showed 42%, 20%, and 11% of hypogonadal etiologies stemming from primary, secondary, and aging, respectively, with the remainder noted as "Unclassified."<sup>279</sup>

In a medical claims database study, it was reported that about 10% of patients on TRT had a diagnosis where a specific cause of hypogonadism was identified, such as Klinefelter syndrome.<sup>278</sup> To the TRT Sponsors' knowledge, there have been no studies that examine the accuracy of diagnosis ICD-9 coding in hypogonadism, so it is possible that some diseases were present but miscoded.

In terms of signs and symptoms, the results from a recent qualitative survey of 95 patients who received TRT indicated that the most frequent symptoms that led to testosterone treatment were erectile dysfunction (66.3%), fatigue (59.0%), and decreased sexual drive (57.9%). These rates are supported by another qualitative structured interview survey by Gelhorn et al evaluating 57 patients receiving TRT.<sup>130,131</sup>

## **5.7                      Reported Diagnostic Codes for Patients Who Receive Testosterone Replacement Therapy**

The TRT Sponsors evaluated reported diagnostic codes for patients who received TRT by conducting a database analysis. In terms of diagnostic codes related to hypogonadism in patients who received TRT, in one database study, 43% of patients had a diagnosis code indicative of hypogonadism at any time during the period of observation. In an unknown percentage of patients, a previous diagnosis for hypogonadism may have been recorded prior to the patient's entry to the data base.

An analysis of the SHA IDV database is reported below:

AbbVie conducted an analysis of the most frequent diagnoses in men receiving TRT using the SHA database. SHA's IDV is a longitudinal patient database that integrates US health care claims data from physician practices, pharmacies, and hospitals. The data set captures more than 4.2 billion health care transactions annually and includes claims for commercial as well as Medicare- and Medicaid-covered patients ([Appendix E](#)).

The most frequent diagnoses in men receiving TRT from SHA database are presented in [Table 21](#), which represents data from 2006 to May 2014. Included in the list of most frequent diagnoses are "other testicular hypofunction" and "malaise and fatigue," the latter possibly being related to hypogonadism. Conditions such as hypertension and hyperlipidemia also appear in the table as being frequent and are comorbid conditions frequently associated with hypogonadism.

**Table 21. Most Common Diagnosis Codes for Patients with a Testosterone Replacement Therapy Prescription (2006 to May 2014, N = 2,923,500)**

Diagnosis Code	Description	Number of Patients
401.9	Unspecified essential hypertension	1,216,393
257.2	Other testicular hypofunction	1,196,709
272.4	Other and unspecified hyperlipidemia	1,191,424
780.79	Other malaise and fatigue	935,817
401.1	Benign essential hypertension	913,382
V70.0	Routine general medical examination at a health care facility	851,612
786.5	Unspecified chest pain	736,124
724.2	Lumbago	712,375
272	Pure hypercholesterolemia	683,196

Data source: SHA's Integrated Dataverse

Note: Common diagnosis codes could be biased by the incidence/prevalence of the condition.

In the Testim<sup>®</sup> Registry, which included men with hypogonadism, it was shown that a proportion of men had comorbid conditions. At baseline, 36.7% of men were determined to have metabolic syndrome, 19.8% had hypertension, 19.9% had dyslipidemia, 17.9% had coronary artery disease, and 12.5% had diabetes.<sup>281</sup>

An additional analysis of the SHA IDV database is reported below.

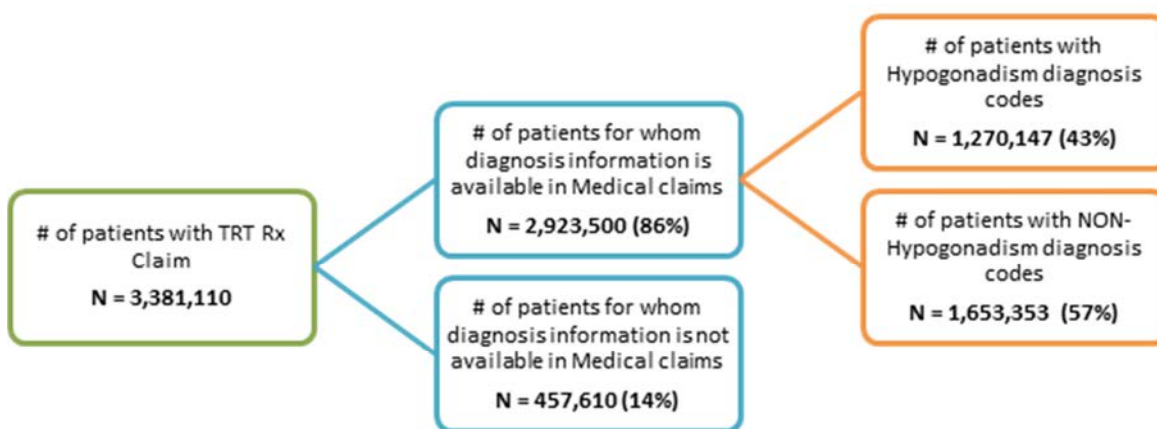
The TRT Sponsors also evaluated the presence of relevant hypogonadism diagnostic codes for patients who received TRT by conducting a database analysis.

AbbVie conducted an additional analysis with SHA using data through May 2014 to determine the frequency of codes related to hypogonadism in patients who received TRT (Figure 9). Of those who received TRT, 86% had at least one diagnosis code for any medical condition. Of these, 43% had a diagnosis code indicative of hypogonadism at any time during the period of observation.

However, the percentage of patients with a relevant diagnosis code may be low in part because, for example, the patient was diagnosed prior to being included

in this analytic data set. Other data sources have reported higher percentages of men receiving TRT who had a relevant diagnosis (Section 5.3).

**Figure 9. Percentage of Claims that Had a Diagnosis of Hypogonadism in Patients Who Received a Prescription of Testosterone Replacement Therapy**



## 5.8 Presence of Testosterone Values Prior to Starting Testosterone Replacement Therapy

The TRT Sponsors evaluated available literature to describe the percentage of patient who had documented baseline serum testosterone values prior to beginning TRT.

The percentage of patients receiving TRT who have baseline serum testosterone laboratory values is variable in the literature, making it difficult to make a conclusion. Rates as high as 91% of men having baseline testosterone level have been reported, although other studies report lower rates of 60% and one study even found a rate as low as 16%.

Of note, the studies discussed below are generally retrospective and may have limitations that could affect the accuracy of their estimates. For example, in some medical record data bases, a laboratory value may have been ordered by a specialist who does not contribute to the data set. If medical claims are used, a laboratory value may have been



obtained prior to the person's entry into the data set. Nonetheless, examining findings from these studies can provide insight about the availability of laboratory values in these data sources.

Relevant literature includes the studies described below:

The characteristics of TRT patients in a managed care setting were described in a recently published abstract.<sup>282</sup> In a study of 10,159 patients treated with TRT in the Kaiser Permanente system, 91% of the patients had baseline levels of serum testosterone prior to starting therapy. The mean serum testosterone level was reported to be  $259.7 \pm 179.5$  ng/dL. Follow-up testosterone levels were available in 59.8% of patients, and at follow-up, these men had a mean testosterone level of  $395.0 \pm 275.3$  ng/dL. Most frequent diagnoses of the sample at baseline were as follows: 43.7% had hypertension, 43.1% had hyperlipidemia, 33.5% had erectile dysfunction, 26.7% had testicular dysfunction, and 20.3% had diabetes.

After an evaluation of US large medical claims (Truven Marketscan Database) and UK electronic medical records (CPRD database), researchers reported that 40.2% of US patients and 53.8% of UK patients did not have a testosterone laboratory measurement in the 180 days prior to TRT initiation.<sup>283</sup>

In a large US data set of new users, 74.7% of the men who received TRT had evidence of a laboratory value for testosterone in the year prior to treatment.<sup>273</sup>

Investigators from Manitoba, Canada found that only 16.9% of the 902 men, who had a least 2 prescriptions for testosterone, had a laboratory value for testosterone during the period of observation (01 April 2000 through 31 March 2003).<sup>284</sup>

In a study by Layton et al, 410,019 men in the US and 6,858 men in the UK were identified who initiated TRT from 2000 – 2011. In this study, more men in the US were found to have eugonadal testosterone levels when tested, whereas in the UK a higher percentage of men had hypogonadal levels when tested. Also, in the US, 4% to 9% of men with normal testosterone levels were given TRT, compared with only 1% of men in the UK.<sup>283</sup>

## **5.9 Persistence of Testosterone Replacement Therapy Use**

The TRT Sponsors evaluated information about the length of treatment for TRT utilizing available literature. The data indicate that the typical length of treatment for testosterone products is between 3 and 4 months. However, the generalizability of these findings is not known.

Relevant literature includes the studies described below:

In the study by Baillargeon et al, the median number of days covered by androgen prescriptions in the 12 months following initiation of treatment in 2010 was 150 days.<sup>273</sup>

In another study, the percentage of patients still on therapy after 3 months was 52% for topical TRT and 31% for short-lasting TRT injections. Patients who restarted therapy after 30 days were defined as cyclic, but this group of patients also showed a relatively high rate of attrition, about 40% to 50% per cycle.<sup>285</sup>

## **5.10 Summary of Utilization Data**

The TRT Sponsors reviewed information regarding usage patterns for TRT, including trends in prescribing patterns of testosterone products, as well as characteristics of patients receiving TRT, such as demographics, reasons for use, prevalence of laboratory testing for testosterone, and length of treatment via available literature and results from the analysis of two data sets.

One data set, containing information on prescriptions, was the IMS NPA, which includes both what the provider prescribes in the retail setting and what is ultimately dispensed to consumers. The other was the SHA, a longitudinal patient database that integrates US health care claims data from physician practices, pharmacies, and hospitals.

Overall, key findings from this review included:

Consistent increases in the monthly number of prescriptions from January 2000 to July 2014, were observed from just over 55,000 in 2000 to over 546,000 in 2014, an approximate 8.8-fold increase in the number of prescriptions during this period of observation.

Recent data show that the majority of prescriptions (approximately 60%) are provided by PCP. Endocrinologists and urologists combined accounted for approximately 22% of the prescriptions.

The highest number of TRT prescriptions, approximately 60%, are observed in the 45 to 64 year old age groups, a trend that has not changed in the past few years. Men younger than 45 years represent approximately 19% of prescriptions, while men older than 65 years represent approximately 21% of prescriptions.

Data characterizing the etiology of hypogonadism in patients receiving TRT and/or baseline signs or symptoms are limited and make it difficult to draw any clear conclusions. A study that evaluated results from a qualitative survey of 95 men receiving TRT, indicated that erectile dysfunction (66.3%), fatigue (59.0%), and decreased sexual drive (57.9%) were the most frequent signs and symptoms observed. However, the generalizability of this information is not known.

In terms of diagnostic codes related to hypogonadism in patients who received TRT, in one database study, 43% of patients had a diagnosis code indicative of hypogonadism at any time during the period of observation. In an unknown percentage of patients, a previous diagnosis for hypogonadism may have been recorded prior to the patient's entry to the database.

The percentage of patients receiving TRT who have baseline serum testosterone laboratory values is variable in the literature, making it difficult to draw a conclusion. Rates as high as 91% of men having baseline testosterone level have been reported, although other studies report lower rates of 60% and one study even found a rate as low as 16%.

The typical length of treatment for testosterone products has been reported to be between 3 and 4 months.

## **6.0 Conclusions**

In summary, hypogonadism is an endocrine disorder characterized by absent or deficient testosterone levels along with signs and symptoms of androgen deficiency. A review of the literature found that the totality of data supports benefits with TRT in hypogonadal men when used in a manner consistent with current FDA-approved product labeling and treatment guidelines.

Guidelines, such as those developed by the Endocrine Society, provide recommendations on how to appropriately identify and evaluate men for hypogonadism, determine whether they are candidates for TRT, and on how to manage them while on therapy.

Product labeling, for TRT, characterizes current knowledge of CV risk. A thorough review of the available TRT literature found insufficient evidence to support an association between testosterone use and an increased risk of CV events. However, the TRT Sponsors also recognize continued active surveillance is required given the questions raised, particularly in certain subpopulations, such as elderly men and/or patients with preexisting CV disease. Ongoing research may provide additional information, such as the Testosterone Trial (T Trial), a study that is designed to characterize the benefits of testosterone use in older men and may also provide relevant information on safety.

The TRT Sponsors reviewed information regarding usage patterns for TRT, including trends in prescribing patterns of testosterone products, as well as characteristics of patients receiving TRT. It was observed that TRT prescriptions have consistently increased from 2000 through 2014, with an approximate 8.8-fold increase in the number of prescriptions during this period of observation. In terms of prescribers, primary care physicians make up the majority of prescribers (approximately 60%).

Men aged 45 to 64 years old received the highest number of prescriptions (approximately 60%). The numbers of prescriptions shown for men younger than 45 years (approximately 19%) and for men older than 65 years (21%) were similar. The typical

length of treatment for testosterone products has been reported to be between 3 and 4 months.

Additional characterization of men using TRT was limited by the ability of the available data sources to address these questions. Some data on etiology of hypogonadism or signs and symptoms is available, but the generalizability of this information is unknown. In terms of diagnostic codes related to hypogonadism in patients who received TRT, in one database study, 43% of patients had relevant diagnostic code indicative of hypogonadism; but this study has limitations that may make this a conservative estimate. The percentage of patients receiving TRT who have baseline serum testosterone laboratory values is variable in the literature with several reports suggesting rates of 60% to 91%, although one study found a rate as low as 16%.

In summary, limitations in the available utilization data make it difficult to fully characterize the population of men taking TRT and to evaluate the degree to which the current use aligns with approved labeling. Specifically, the utilization data lack diagnostic codes for indications. Further, the data suggests that the practice of laboratory testing including pre- or post-testosterone serum levels is inconsistent.

The TRT Sponsors remain committed to educating clinicians and patients on the benefits and risks of TRT so that they can make informed treatment decisions. To maximize the benefits of TRT and mitigate potential risks, the TRT Sponsors propose the following for further discussion at the September Advisory Committee:

The TRT Sponsors will partner with professional societies (such as the Endocrine Society) regarding current practices for diagnosis, patient selection, and management, and will continue communicating and educating clinicians and patients on the appropriate use of these products. Further efforts could include targeted training (for instance, to select prescriber groups) and, if appropriate, revising product labeling.

The scientific understanding of benefits and risks, broadly and in special populations, continues to advance. Guidelines for TRT use may be further refined as new data become available.

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## Appendix A. Cardiovascular Events in the General Population

**Table A1. Cardiovascular Events in the General US Population, Males and Females**

	Prevalence, %	Incidence per 1,000 Person Years	Deaths per 100,000 Population
Cardiovascular disease			262.5
20 years old	36.9		
Myocardial infarction			
20 years old	3.6		
Coronary heart disease			134.9
20 years old	7.9		
White	7.9	4.0	
Black	7.9	5.1	
Hypertension			17.8
20 years old	33.6		
White	28.1		
Black	41.4		
Heart failure			89.2
20 years old	2.6	2.19	
Stroke			43.6

Source: Values for prevalence, incidence, and deaths are reported in Lloyd-Jones et al (2010). An additional source for death values is the American Heart Association Fact Sheet (2010a).

**Table A2. Cardiovascular Events in the Male Population**

<b>Event/Region</b>	<b>Prevalence, %</b>	<b>Incidence per 1,000 Person Years</b>	<b>Deaths per 100,000 Population</b>
Cardiovascular disease			313.3
United States			
Age, years			
< 20	37.9		
20 – 39	14.9		
40 – 59	39.6		
60 – 79	73.6		
80	78.8		
35 – 44		3.0	
45 – 54		10.1	
55 – 64		21.4	
65 – 74		34.6	
75 – 84		59.2	
80 – 94		74.4	
85 – 94		74.0	
Race			
White	38.1		306.6
Black	44.6		422.8
Mexican-American	28.5		

See notes at end of table.

**Table A2. Cardiovascular Events in the Male Population (Continued)**

Event/Region	Prevalence, %	Incidence per 1,000 Person Years	Deaths per 100,000 Population
Heart Failure			
Age, years			
United States			
White			
20	3.2	6.0	103.7
65 – 74		15.2	
75 – 84		31.7	
85		65.2	
Black			
20	3.0	9.1	105.9
65 – 74		16.9	
75 – 84		25.5	
85		50.6	
Worldwide			
20 – 24		0.33	
25 – 29		0.50	
30 – 34		0.84	
35 – 39		1.27	
40 – 44		2.03	
45 – 49		4.06	
50 – 54		6.92	
55 – 59		11.33	
60 – 64		17.37	
65 – 69		34.99	
70 – 74		48.22	
75 – 79		85.55	
80 – 84		114.30	
85		172.45	

See notes at end of table.

**Table A2. Cardiovascular Events in the Male Population (Continued)**

Event/Region	Prevalence, %	Incidence per 1,000 Person Years	Deaths per 100,000 Population
Myocardial Infarction/Acute Coronary Syndrome			
Age, years			
United States			
White	5.1	3.9	
35 – 44		0.9	
45 – 54		3.0	
55 – 64		6.1	
65 – 74		9.2	
Black	3.6	4.2	
35 – 44		1.2	
45 – 54		3.5	
55 – 64		6.2	
65 – 74		10.3	
Worldwide			
20 – 24		0.13	
25 – 29		0.25	
30 – 34		0.36	
35 – 39		0.69	
40 – 44		1.36	
45 – 49		3.02	
50 – 54		4.34	
55 – 59		5.35	
60 – 64		6.61	
65 – 69		8.40	
70 – 74		10.16	
75 – 79		14.2	
80 – 84		15.57	
85		17.26	

See notes at end of table.

**Table A2. Cardiovascular Events in the Male Population (Continued)**

<b>Event/Region</b>	<b>Prevalence, %</b>	<b>Incidence per 1,000 Person Years</b>	<b>Deaths per 100,000 Population</b>
Coronary heart disease	9.1		
United States			
White	9.4	12.5	176.6
Black	7.8	10.6	206.4
Hispanic	5.3		
Stroke	2.3 – 3.8		
Age, years			
United States			
20 – 39	0.3		
40 – 59	1.0		
60 – 79	7.4		
80	15.4		
Race			
United States			
White			41.7
Black			67.1
Hispanic			35.9
Hypertension	34.4		
Age, years			
United States			
20 – 34	12.2		
35 – 44	24.4		
45 – 54	38.8		
55 – 64	53.2		
65 – 74	65.4		
75	64.6		

See notes at end of table.



**Table A2. Cardiovascular Events in the Male Population (Continued)**

Event/Region	Prevalence, %	Incidence per 1,000 Person Years	Deaths per 100,000 Population
Hypertension, continued			
Race			
United States			
White	34.3		15.6
Black	43.0		51.1
Hispanic	25.9		

Sources: Lloyd-Jones et al (2010), American Heart Association (2010b), PatientBase, acute heart failure (2014), and PatientBase, acute coronary syndrome (2014).

\* Cardiovascular disease includes hypertension, stroke, heart failure, angina pectoris and coronary artery disease/myocardial infarction.

\*\* Myocardial infarction / acute coronary syndrome includes ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, and unstable angina.

## Appendix B. Summary of Studies Discussed Within the Cardiovascular Risk Section

Author	Setting	Study Design	Inclusion Criteria	Formulation/Dose	N	Age, years (mean)	Outcome
<b>Placebo-Controlled Studies</b>							
<i>Studies not showing an association between TRT and CV events</i>							
Srinivas-Shankar 2010	US	Randomized, double-blind, placebo-controlled, parallel-group	TT 345 ng/dL or FT 250 pmol/L	Transdermal T gel 1% 50 mg/day	274	> 65 (73.7)	TG, LDL, and HDL unchanged in both groups.
Kenny 2010	US	Randomized, double-blind, placebo-controlled	Total T < 350 ng/dL or BAT at least 1.5 SDs lower than young adult mean (95 – 350 ng/dL); history of fracture or BMD T-score < –2.0 and frailty	Transdermal T gel 1% 50 mg/day	131 (69 TRT, 62 placebo)	TRT: 77.9 ± 7.3 Placebo: 76.3 ± 8.0 (mean 77.1)	No differences in rates of CV events between the TRT and placebo groups.
Hildreth 2013		Randomized, placebo-controlled trial of TRT crossed with progressive resistance training (3 times/wk vs none)	Generally healthy older men with low – normal baseline total T levels (200 – 350 ng/dL)	Transdermal T gel 1% 2.5 – 5 mg/day	167 (96 TRT, 47 placebo)	66 ± 5	Fewer serious CV events in the TRT group (3%) than placebo group (21%).

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Author	Setting	Study Design	Inclusion Criteria	Formulation/Dose	N	Age, years (mean)	Outcome
<i>Studies showing an association between TRT and CV events</i>							
Basaria 2010 (TOM trial)	US	Randomized, double-blind, placebo-controlled, parallel-group	Free T, TT 100 – 350 ng/dL or FT < 50 pg/mL	Transdermal T gel 1% 100 mg/day	209	> 65 (74)	CV-related events higher in TRT group; terminated early. CV-related events included chest pain, syncope, BP.
Meta-analysis							
<i>Studies not showing an association between TRT and CV events</i>							
Calof 2005	--	Meta-analysis of 19 randomized clinical trials	Low or low-normal T levels	Any formulation; TRT duration 90 days	651 TRT; 433 placebo	45+	No significant differences in rates of CV events between the TRT and placebo groups (OR 1.14; 95% CI: 0.59, 2.20).
Fernandez-Balsells 2010	--	Meta-analysis of 51 randomized and nonrandomized placebo-controlled trials	Low or low-normal T levels	Any formulation; TRT duration of 3 months		Any	No significant differences in rates of death, MI, revascularization procedures or cardiac arrhythmias between the T and placebo groups. T treatment associated with significant increase in Hgb and Hct and decrease in HDL.
Haddad 2007	--	Meta-analysis of 30 randomized placebo-controlled trials (6 for CV events)	Low T: TT 300ng/dL, also included normal or low – normal T level groups	Any T formulation	1,642 men (808 TRT); those reporting CV events: 161 TRT, 147 controls	Any	No increased risk of CV events following initiation of TRT.

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Author	Setting	Study Design	Inclusion Criteria	Formulation/Dose	N	Age, years (mean)	Outcome
Ruige 2013	--	Meta-analysis of 10 randomized placebo-controlled trials	Low T	Any T formulation	2,137 men (1,289 TRT; 848 placebo)	Range 18 to >80	No statistically significant difference between placebo and testosterone treatment was found for testosterone treatment and CV risk (relative risk = 1.64; 95% CI: 0.77, 3.47).
<i>Studies showing an association between TRT and CV events</i>							
Xu 2013	--	Meta-analysis of 27 placebo-controlled randomized trials	Low T and/or chronic diseases; initial T levels ranged from 7.3 – 21.1 nmol/L	Any T formulation	2,994 (1,733 TRT, 1,261 placebo)	Range 18 to > 80	Increased risk of vascular events in the TRT population (OR 1.54, 95% CI: 1.09, 2.18); however, only 1 of the 27 studies found a statistically significant increase.
<b>Observational Studies</b>							
<i>Studies not showing an association between TRT and CV events</i>							
Shores 2012	7 VA centers	Retrospective, observational	Serum total T level 250 ng/dL or less	IM 88.6%, patch 9.1%, gel 2.3%	1,031; TRT initiated in 398; median time to initiation = 3.3 mo; duration of TRT median = 16.6 mo, mean = 16.7 mo	40+	T-treated men had a 39% reduction in mortality risk (HR 0.61; 95% CI: 0.42, 0.88), compared with untreated men.
Brooke 2012	Clinical practice	Long-term retrospective audit	TRT	Any; 84% received T gel	401 (1642 PY TRT)	58.7±14.3 years	TRT was not associated with an increase in MACE or mortality.
Baillargeon 2014	Medicare	Observational	Received at least 1 TRT injection	IM	6,355 TRT; 19,065 matched non-user	> 66	TRT was not associated with an increased risk of MI (HR = 0.84; 95% CI 0.69, 1.02).

Testosterone Replacement Therapy  
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Author	Setting	Study Design	Inclusion Criteria	Formulation/Dose	N	Age, years (mean)	Outcome
<i>Studies showing an association between TRT and CV events</i>							
Vigen 2013	VA	Retrospective, observational	Men who had undergone coronary angiography and had low T levels	Any	8,709; 1,223 started TRT	Mean 60.6	After adjusting for the presence of CAD, TRT use as a time-varying covariate was associated with increased risk of adverse outcomes (HR 1.29; 95% CI: 1.04, 1.58; $P = 0.02$ ). TRT started after a median of 531 days (IQR, 229-894 days) following coronary angiography.
Finkle 2014	Electronic health records	Retrospective, observational	Men 65 years of age and men 65 years of age with and without a history of heart disease	Any	Over 55,000 patients with a claim for testosterone prescription	> 65 and < 65	Patients > 65 years had an increased risk (RR = 2.17, 95% CI: 1.27, 3.77) of AMI in the post-TRT period compared to the period prior to treatment. Patients < 65 with a history of heart disease showed an elevation in risk after TRT (RR = 2.9, 95% CI: 1.49, 5.62).

AMI = acute myocardial infarction; BAT = bioavailable testosterone; BMD = bone mineral density; BP = blood pressure; CAD = coronary artery disease; CI = confidence interval; CV = cardiovascular; FT = free testosterone; Hct = hematocrit; HDL = high-density lipoprotein cholesterol; Hgb = hemoglobin; HR = hazard ratio; IM = intramuscular; IQR = interquartile range; LDL = low-density lipoprotein cholesterol; MACE = major adverse cardiac events; MI = myocardial infarction; OR = odds ratio; PY = patient years; RR = relative risk; SD = standard deviation; T = testosterone; TG = triglycerides; TOM = Testosterone in Older Men; TRT = testosterone replacement therapy; TT = total testosterone; US = United States; VA = Veterans Affairs

## Appendix C. Summary of Studies Reporting Effects of Testosterone Replacement Therapy on Lipids, Cholesterol, and Triglycerides

Author	Major Findings for lipids, LDL, HDL, triglycerides, cholesterol
Haider 2014	<ul style="list-style-type: none"> <li>• TRT improved lipid profiles in a long-term, cumulative, uncontrolled, observational registry study of obese hypogonadal men with T2DM treated with testosterone undecanoate injections for up to 6 years.</li> <li>• TRT significantly reduced total cholesterol, LDL cholesterol and triglycerides and increased HDL cholesterol levels.</li> <li>• The mean changes in lipid profiles were gradual and progressive, plateauing between 3 and 4 years.</li> </ul>
Haddad 2007	<ul style="list-style-type: none"> <li>• In patients with low levels of baseline testosterone, exogenous testosterone did not affect any of the lipid sub-fractions.</li> <li>• In patients with normal levels of baseline testosterone, exogenous testosterone resulted in a significant decrease in total cholesterol levels.</li> <li>• In patients with normal levels of baseline testosterone, exogenous testosterone did not affect the levels of LDL, HDL, or triglyceride levels.</li> <li>• In patients with chronic disease or in those on glucocorticoid therapy, exogenous testosterone resulted in a small decrease in levels of HDL cholesterol.</li> <li>• In patients with chronic disease or in those on glucocorticoid therapy, exogenous testosterone did not affect the levels of total cholesterol, LDL cholesterol, or triglycerides.</li> </ul>
Whitsel 2001	<ul style="list-style-type: none"> <li>• Exogenous testosterone resulted in small but significant reduction in the levels of total, LDL, and HDL cholesterol.</li> <li>• Exogenous testosterone did not affect triglyceride levels.</li> </ul>
Isidori 2005	<ul style="list-style-type: none"> <li>• Exogenous testosterone resulted in reduced levels of total cholesterol.</li> <li>• The improvement in total cholesterol was more significant for patients with reduced levels of baseline testosterone.</li> <li>• No significant change in total cholesterol in patients with baseline testosterone of &gt; 10 nmol/L.</li> <li>• Exogenous testosterone did not affect levels of LDL or HDL cholesterol.</li> <li>• The effect of testosterone replacement therapy on triglyceride levels was not examined in this meta-analysis.</li> </ul>
Calof 2005	<ul style="list-style-type: none"> <li>• Exogenous testosterone did not affect lipid levels (meta-analysis)</li> </ul>
Hellstrom 2012	<ul style="list-style-type: none"> <li>• Exogenous testosterone did not affect lipid levels</li> </ul>
Brooke 2012	<ul style="list-style-type: none"> <li>• Exogenous testosterone resulted in reduced levels of lipid and cholesterol levels.</li> </ul>

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Author	Major Findings for lipids, LDL, HDL, triglycerides, cholesterol
Rao 2013	<ul style="list-style-type: none"><li>• Exogenous testosterone resulted in reduced levels of total cholesterol, triglycerides and LDL levels.</li><li>• Exogenous testosterone resulted in a modest decrease in levels of HDL cholesterol</li></ul>
Saad 2011 Haider 2010	<p>Systematic analysis of the time-course of the spectrum of biological effects of testosterone on the various target systems</p> <ul style="list-style-type: none"><li>• Lipids: Effects on lipids appear after 4 weeks, maximal after 6 to 12 months.</li><li>• Total cholesterol and triglycerides: Decreases in serum total cholesterol and serum triglycerides have been observed after 1 to 3 months, with maximum effects observed after 12 months.</li><li>• LDL: The decrease in low-density lipoprotein cholesterol seems somewhat slower ranging from 3 to 12 months with a maximum observed after 24 months.</li><li>• HDL: Increases in high-density lipoprotein cholesterol have been observed after 3 months, with a continuous increase over 24 months. However, some studies have observed a decrease in HDL.</li></ul>

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HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; T2DM = type 2 diabetes mellitus; TRT = testosterone replacement therapy

## **Appendix D. Description of the National Prescription Audit**

The National Prescription Audit™ (NPA) is an industry standard source of national prescription activity for all pharmaceutical products. NPA measures demand for prescription drugs, including both what the provider prescribes in the retail setting and what is ultimately dispensed to consumers across four unique channels. From the selected pharmacies, IMS collects new and refilled prescription for every day of the month. Data are available on a monthly and weekly basis at varying levels of depth. For example, data can be analyzed and stratified by patient age, patient gender, co-payment, and four methods of payment. NPA is useful to address a variety of research topics examining pharmaceuticals, especially investigations that focus on prescription drug utilization, Rx size, average consumption, and more than 90 prescriber specialty groupings representing over 170 specialties. The NPA represents and captures over 70% of all prescription activity in the United States, including Alaska and Hawaii, and covers all products, classes, and manufacturers. Although the NPA provides data at a national level, data that is summarized into the NPA is also available at more granular geographic levels. This product, the IMS Health Xponent™ database, is described separately.

### **DATA SAMPLE**

From the universe of retail, standard mail service, specialty mail service and long-term care pharmacies, IMS selects a representative sample stratified by geographic location.

### **Universe**

The pharmacy universe is comprised of more than three billion prescriptions from retail, mail service, and long-term care pharmacies. NPA estimates in 2011 are based on a universe of approximately 57,000 retail pharmacies (including chain/mass merchandisers, independent, and food-store pharmacies), 327 non-governmental mail service pharmacy outlets, and ~3,000 long-term care facilities, including nursing homes and nursing home providers. Data collected from HMOs that serve HMO members only, dispensing physicians, hospital pharmacies, home health care, and clinic pharmacies are not included.



### **Sample**

As of 2011, NPA includes 38,000 retail stores and collects randomly drawn and electronically submitted retail pharmacy data for new and refilled prescription for every day of the month.

All mail service pharmacy outlets are invited to participate and most participating outlets are used in the sample. As of 2011, NPA™ includes approximately 119 mail service pharmacy outlets. Finally, the NPA™ sample also includes approximately 820 long-term care facilities. Alternative data sources are used to enhance the accuracy of the audited data and to allow for robust national projections.

([http://www.imshealth.com/deployedfiles/ims/global/content/insights/researchers/npa\\_data\\_brief.pdf](http://www.imshealth.com/deployedfiles/ims/global/content/insights/researchers/npa_data_brief.pdf). Accessed on: 10 July 2014).

## Appendix E. Testosterone Replacement Therapy Prescription Volume by Specialty Group, 2009 – May 2014

	2009	2010	2011	2012	2013	2014 YTD
Total	3,875,670	4,413,978	5,270,336	6,884,323	7,458,437	2,776,672
PCP	2,323,555	2,672,231	3,231,028	4,322,610	4,648,970	1,702,685
Family practice	964,890	1,138,818	1,410,007	1,944,778	2,125,265	784,875
General practice	36,796	41,491	49,936	64,853	66,027	23,929
Internal medicine	926,453	1,032,897	1,202,800	1,532,331	1,612,502	581,891
Osteopathic medicine	395,416	459,025	568,285	780,648	845,176	311,990
Endocrinology	448,206	490,168	552,266	655,659	684,787	261,822
Urology	522,514	586,353	677,105	849,773	925,370	346,538
All Other	581,395	665,226	809,937	1,056,281	1,199,310	465,627
Addiction medicine	3,233	3,113	2,849	2,969	3,036	1,067
Allergy	20	14	16	10	22	1
Allergy/diagnostic lab immunology	14,185	17,083	19,173	22,837	22,341	7,765
Anesthesiology	19,248	21,612	25,719	34,474	34,586	11,831
Cardiology	584	628	870	830	737	271
Cardiothoracic surgery	11	11	21	30	50	26
Cardiovascular surgery	576	633	636	915	969	303
Clinical neurophysiology	14	24	33	34	31	19
Clinical pharmacology	61	50	54	123	106	28
Colon and rectal surgery	110	156	311	301	425	167
Critical care medicine	681	615	586	793	959	366
Dentistry	3,374	4,128	5,061	6,179	4,574	1,523
Dermatology	1,856	2,024	2,322	3,050	2,867	909
Dermato-pathology	23	31	42	23	17	10
Emergency medicine	15,841	19,576	24,051	33,362	36,918	13,328
Gastroenterology	8,526	8,777	9,517	11,090	11,090	3,851
General preventive medicine	2,830	3,072	3,872	5,127	5,030	1,791
General surgery	8,356	10,458	13,753	19,704	22,206	8,499
Genetics	147	114	71	116	126	37
Geriatric psychiatry	86	72	147	117	158	53
Geriatrics	12,015	13,675	15,543	20,768	23,798	9,336
Hematology	3,923	3,633	3,281	3,868	3,561	1,122
Hepatology	126	133	166	177	159	64
Hospice and palliative med	-	-	6	26	79	33

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Advisory Committee Briefing Document

	2009	2010	2011	2012	2013	2014 YTD
Immunodiagnostic lab immunology	12	-	2	9	-	-
Infectious diseases	63,272	59,126	60,713	66,327	66,862	25,267
Internal med/pediatric	16,431	20,433	26,693	37,114	40,916	14,460
Medical microbiology	37	58	58	69	31	14
Nephrology	11,339	12,579	14,082	17,384	17,474	5,804
Neurological surgery	1,294	1,454	1,288	1,468	2,178	750
Neurology	7,324	7,683	7,908	9,004	8,574	3,015
Neurosurgery – critical care	-	-	-	-	2	-
Nuclear medicine	169	182	163	147	223	119
Nurse practitioner	100,651	134,390	179,861	271,004	339,161	140,564
Nutrition	587	557	368	347	341	128
Obstetrics/gynecology – critical care	-	-	-	-	-	-
Obstetrics/gynecology	26,724	28,216	31,469	38,068	41,418	16,195
Occupational medicine	2,521	3,322	4,133	4,864	5,349	2,044
Oncology	14,984	15,527	17,006	18,070	17,847	6,280
Ophthalmology	1,336	1,664	1,935	2,447	2,499	967
Optometry	204	206	333	404	295	95
Orthopedic surgery of spine	87	105	104	93	108	32
Orthopedic surgery	3,409	3,759	5,974	5,857	5,809	2,079
Other	7,501	6,773	7,075	7,925	7,713	3,150
Other surgery	1,272	1,312	1,350	1,578	1,864	986
Otolaryngology	2,062	2,223	2,937	3,161	2,934	1,101
Otology	-	1	3	15	21	5
Pain medicine	2,566	2,692	3,789	4,184	3,465	1,071
Pathology	1,086	930	833	963	1,361	537
Pediatric critical care	19	6	34	57	59	13
Pediatric neurological surgery	2	-	-	1	5	3
Pediatrics	8,394	9,284	10,440	13,019	13,249	5,122
Pediatrics, diagnostic lab immunology	-	2	-	-	2	-
Physical medicine and rehabilitation	13,151	14,496	17,107	19,782	18,612	6,366
Physician assistant	90,281	117,667	165,620	250,858	302,719	121,535
Plastic surgery	1,217	1,363	1,581	2,115	2,340	1,057
Podiatry	583	758	768	733	763	291
Psychiatry	15,867	16,285	17,269	20,934	21,000	7,404
Psychoanalysis	47	55	82	130	135	76
Pulmonary critical care	3,227	2,984	2,741	3,257	3,251	1,243

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Advisory Committee Briefing Document

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	<b>2009</b>	<b>2010</b>	<b>2011</b>	<b>2012</b>	<b>2013</b>	<b>2014 YTD</b>
Pulmonary diseases	11,556	11,956	13,318	16,454	16,639	5,674
Radiology	303	425	544	740	795	293
Rheumatology	5,656	6,171	6,956	8,375	8,543	2,833
Sleep medicine	5	2	22	27	58	47
Specialty unspecified	66,867	66,543	71,218	52,458	59,156	22,032
Sports medicine	2,902	3,586	5,098	8,611	10,321	3,946
Surgery, critical care	12	15	18	44	31	15
Thoracic surgery	139	182	299	383	445	188
Veterinary medicine	473	622	645	878	897	426

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Data source: IMS NPA [Projected TRx].

Note: 2014 is YTD data (January 2014 – May 2014).

## **Appendix F. Description of SHA's Integrated Dataverse (IDV)**

SHA's Integrated Dataverse (IDV) is a longitudinal patient database that integrates US health care claims data from physician practices, pharmacies, and hospitals. The data set captures more than 4.2 billion health care transactions annually and includes claims for commercial as well as Medicare- and Medicaid-covered patients.

Prescription transactions also include assistance program providers and cash payments. The database contains approximately 3.1 billion paid, non-reversed prescriptions claims (73% of all retail prescriptions and 65% of all mail order prescriptions) linked to over 220 million unique patients.

Of these, approximately 65% of patients have 2 or more years of prescription drug history. Claims from hospital and physician practices include over 169 million patients annually, representing 51% of professional service claims and 25% of hospital / institutional claims in the US. The professional and institutional claims provide CPT/HCPCS medical procedure history as well as ICD-9 diagnosis history. Nearly three-fourths (72%) of prescription patients can be linked to a diagnoses and/or medical procedure record. The overall sample includes 1.6 million health care practitioners and 2,600 pharmacy benefit payers (representing more than 9,000 health plans).

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